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THE DETERMINATION OF THE EQUILIBRIUM IN THE HUMAN BODY BETWEEN ACIDS AND BASES WITH ESPECIAL REFERENCE TO ACIDOSIS AND NEPHROPATHIES.*

By Andrew Watson Sellards,

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OUTLINE.

I. Maintenance of Normal Equilibrium:
   1. By food supply;
   2. By elimination (especially from the kidneys and lungs);
   3. By the formation of ammonia from protein.
II. Maintenance of Equilibrium in Conditions of Acidosis:
   1. By utilization of the reserve supply of fixed bases of the tissues;
   2. By increased elimination;
   3. By the increased formation of ammonia.
III. General Method for Detecting Disturbances of this Equilibrium by the Determination of the Tolerance of the Body to Bases:
   1. In normal individuals;
   2. In acidosis;
   3. In unknown conditions.
IV. Summary:
   1. Behavior in diabetes;
   2. Interpretation of ammonia coefficient;
   3. Behavior in various nephropathies.

In order to meet the changing conditions of our environment and to control the series of alterations which are continually taking place within the body, we find that a normal equilibrium, in many instances, is maintained by means of balanced mechanisms. These mechanisms affect various systems of the body and they involve both physical and chemical reactions. Some of the better known examples are the heat regulating mechanism and the balance between water and salts to maintain a normal osmotic pressure. It will also be remembered that many diverse chemical processes taking place within the body are closely dependent upon a delicate adjustment of the reaction of their medium and it is found that the concentration of acids and bases in the body fluids remains comparatively constant in the presence of many normal and pathologic factors which tend to disturb this equilibrium. The compensation which is maintained is sufficiently effective, except in extreme conditions, to prevent any pronounced change in the reaction of the body fluids even though extensive metabolic changes may be taking place within the body. Thus a very considerable increase in the acid end-products of metabolism may be accompanied by only a slight change in the values obtained by titration for the acidity of the urine and the alkalinity of the blood. Therefore, other methods, in addition to the examination of the body fluids, must be used to detect the full extent of the changes which are taking place in the body and it is the purpose of this paper to consider such methods.

General Considerations.

Normal Equilibrium.—Under normal conditions, upon a mixed diet, there is a continuous interchange in the body between acids and bases. The food supply yields a limited

* From the Chemical Division of the Medical Clinic.

amount of bases, but the acid forming substances usually predominate, the proteins yielding considerable acid on account of their content in sulphur and phosphorus. Two important methods suffice to compensate for the excess of acids over bases that ordinarily occurs in a mixed diet. The adjustment of the smaller variations appears to be very effectually controlled by the kidney; either acid or base is promptly excreted, according as one or the other is present in excess in the blood stream. Thus, although the reaction of the blood is constantly alkaline, the kidney in the formation of urine, is able to separate the acids from their combinations with the bases, excreting acid salts and retaining the bases, in part at least, in the blood. This function of the kidney apparently represents one of the important activities of this organ, but the exact process is but little understood.

Ordinarily there is a constant excretion of moderate quantities of ammonium salts in the urine, and this is usually interpreted as indicating that a slight grade of acidosis exists even under normal conditions. One objection which has been advanced against this view is that traces of ammonia continue to appear in the urine even though its reaction is kept constantly alkaline by the administration of carbonates. Furthermore the quantities of sodium bicarbonate which are required to reduce materially the normal output of ammonia are considerably in excess of the calculated values. An examination of the data recently reported by Janney[1] illustrates this characteristic. Perhaps these two features may be explained on a common basis. But whatever their explanation may be, the consensus of opinion is that practically all of the ammonia which appears normally in the urine has been intercepted in the course of urea formation for the neutralization of acids.

Pathologic Conditions.—The means by which the body compensates for pathologic excesses of acid consist essentially in a quantitative increase in the normal processes of metabolism. The principal compensatory changes are as follows:

I. Increased output in the urine of:
   1. Acid radicals,
   2. Fixed bases, and
   3. Ammonia nitrogen.

In severe grades of acidosis this results in:

II. Decreased content of the blood in:
   1. Fixed bases, and
   2. Carbon dioxide.

These quantitative changes represent general non-specific alterations resulting from the increased accumulation of hydrogen ions. Theoretically, such changes should occur in any acidosis independently of the nature of the acid in question.

The qualitative changes, on the other hand, depend upon the ætiologic factor and are represented, as a rule, by the appearance of a foreign acid; in starvation acidoses, these changes are absolutely qualitative since β-oxybutyric and acetoacetic acid are not found under normal conditions. Likewise, the appearance of acetone from the oxidation of these acids constitutes a change which, for practical purposes, is essentially qualitative in character.

[1] Janney: Ztschr. f. physiol. Chemie, Strassb., 1912, LXVII, 99.

Methods of General Application.

These qualitative and quantitative changes constitute evidence of the disturbance of equilibrium in the content of the body in acid and base. The behavior of acetone and acetoacetic and β-oxybutyric acid has been studied with especial care in the starvation acidoses and the tests for these substances are particularly applicable for the detection of such conditions. However, in the development of the theory of acidosis, it would seem desirable to possess a method which would not be limited to any one acid, but would be of general application.

A consideration of the quantitative changes occurring in acidosis shows that many of them would not afford a suitable basis for the development of a general method. The detection of the increased output of fixed bases in the urine is not particularly feasible as a routine procedure. Moreover, the kidney is able to increase the excretion of acid radicals only to a very limited extent above the normal. Likewise the compensatory processes of the body are usually sufficient to prevent any striking diminution in the alkalinity of the blood.

The carbon dioxide content of the blood may show extreme diminution, but apparently this change takes place only in the very advanced stages of acidosis.

Without question, one of the most important sources of bases consists in the formation of ammonia from protein, and the increase in its excretion offers valuable evidence in the detection of acidosis. Theoretically, one would expect an increase in the production of the ammonium salts in any acidosis. However, in the interpretation of the ammonia metabolism there are two considerations which are of primary importance. In the first place one would require to know the sensitiveness with which the body responds by an increase in ammonia production; for when the output is normal, one could exclude the possibility of the presence of an early stage of acidosis only if it were known that a slight increase in acid is accompanied by an increase in ammonia. On the other hand, in making a positive diagnosis on the basis of a high ammonia nitrogen, it is necessary to exclude a primary disturbance of protein metabolism resulting in an increased output of ammonia. Cases illustrating these conditions will be discussed later. In general, it may be said that any signs indicating an hepatic lesion would complicate the interpretation of the ammonia metabolism. Even in diabetes the nitrogen partition in the urine does not always behave merely as a secondary disturbance of metabolism. Thus if the increase in ammonia were a purely compensatory process, it should cease when a liberal supply of base is provided. However, especially among advanced cases, instances not infrequently occur in which this increase continues in the presence of an abundance of carbonates.[2] Under certain

[2] von Noorden considers that a primary disturbance of protein metabolism may occur in diabetes. His evidence is based on an increase in the output of purin nitrogen.

conditions, therefore, it may be difficult to determine whether an increased ammonia coefficient represents a purely compensatory process or whether it also involves a primary disturbance in the nitrogen metabolism.

On theoretical grounds it would seem that the behavior of the body toward the fixed bases would supplement the conclusions derived from the data concerning the production of ammonia. We have, therefore, two procedures which apparently would be applicable in any acidosis, namely, (1) the study of the ammonia excretion, and (2) the fate of the fixed bases upon introduction into the body. As regards the relationship between these methods, the features which present themselves more prominently for consideration are the relative sensitiveness of these two procedures and the effect of various complicating factors upon the interpretation of the results which they yield. Accordingly, I have undertaken the study of the effect of the administration of bases with a view to the development of a method for determining the state of equilibrium in the body between acids and bases. This has been undertaken, not so much from a chemical or physico-chemical point of view, but rather by the use of methods which involve physiological reactions.

Ordinarily, the body conserves its supply of base with considerable care. Thus in the lungs the carbon dioxide is liberated from the acid carbonates and is excreted as such; in the kidneys the acid radicals, which have been neutralized by bases, are again converted into acid salts. In both instances the bases, in part at least, are retained in the body. The method which was adopted to establish the normal conditions of equilibrium consisted in the determination of the quantity of base which it is necessary to introduce into the body in order to bring about its excretion in the urine. Of the many procedures which might be suggested this one has afforded a satisfactory basis for determining the point at which the body contains an excess of bases. An increase beyond the normal in the amount of base which the body can take up might represent, therefore, an increase in the production of acid. On the other hand, the spontaneous excretion of bases does not ordinarily occur in sufficient quantity to indicate a pathologic disturbance.

Determination of Tolerance to Fixed Bases.

In adopting a routine for the determination of the behavior of individuals toward bases under normal and pathologic conditions, the following questions have been considered:

1. Choice of base;
2. Method of administration, and
3. Collection and examination of urine specimens.

In the selection of a suitable base one may consider either the hydroxides themselves or some of the substances which readily give rise to hydroxyl ions upon solution in water, such as the salts of the weak acids, especially carbonic acid. Sodium bicarbonate was chosen in preference to the normal carbonate, sesqui-carbonate, or the hydroxide. Although the carbonate may, perhaps, be more suitable in the therapy of advanced stages of acidosis, yet for diagnostic purposes, where the acidosis may be slight in extent or absent, the bicarbonate seems preferable in order to avoid the caustic properties of the normal carbonate. One might even employ the neutral salts of the organic acids (*e. g.*, sodium acetate) depending upon their oxidation to carbonates, but any involvement of the oxidative processes of the body would introduce complicating factors.

As a general rule, except when large quantities were to be used, a 2 per cent solution of sodium bicarbonate was employed. The following precautions were adopted in order to avoid too extensive loss of carbon dioxide with conversion of the bicarbonate into the carbonate. Sterilization was carried on at a pressure of 10 lbs. for 30 minutes in an atmosphere of carbon dioxide. This was generated by placing a moderate quantity of sodium bicarbonate in the water supplying the autoclave. The sterilizer was always cooled to room temperature before opening. Ordinary cork stoppered bottles were used as containers for the 2 per cent solution. It was found that these bottles could be fairly effectively closed during sterilization by tying the cork stoppers in place. The solutions were kept securely stoppered and were used not later than two or three days after sterilization. Under these conditions sterilization could be readily effected without converting more than 5 to 10 per cent of the bicarbonate into carbonate. This amount of change is not greater than occurs at ordinary temperatures when bicarbonate is dissolved in water. Throughout this paper the term bicarbonate is used to apply to both the salt itself and its solutions, though in the latter a certain proportion of the bicarbonate gives rise to carbonate and hydroxyl ions.

As regards the method of administration, it is desirable that the sodium bicarbonate may be given either by the mouth or by intravenous injection, in order that one may have a choice of procedure according to the individual case under consideration. Thus in some of the cardio-vascular conditions there are complications in which intravenous injections are not suitable. Also, instances may frequently occur in which intravenous injections are unnecessary, inasmuch as the ingestion tests suffice to show that normal conditions exist. The principal disadvantage of ingestion of bicarbonate depends upon the question of assimilation. There would appear to be no reasonable doubt about the assimilation when small amounts are administered and when the condition of the gastro-intestinal tract is normal. This, however, introduces rather important limitations in the quantities which can be employed.

Injection methods are essential if large amounts are to be given or if conditions such as nausea, pyloric obstruction, or diarrhœa exist. By inserting the injection needle directly into the vein without incising the skin, one can introduce comparatively large quantities with a minimal amount of discomfort to the patient.

In the examination of the urine I have used only very simple methods. Quantitative estimations of the amount of carbonates recovered in the urine were not attempted. The rather wide variation in the behavior of the urine toward the various indicators complicates the direct application of titration methods for the determination of alkalinity, and it would seem that no suitable applications of the alkalimetric processes have been developed for the examination of urine. Only qualitative

tests have been employed. With litmus as an indicator it was assumed that, if the urine is definitely acid, there can be no carbonate or bicarbonate present. One point, however, is essential, namely, that specimens which are only slightly acid should be thoroughly boiled, since the bicarbonate may be excreted as such and it reacts less readily with litmus than normal carbonate. Thus, it frequently happens that a specimen of urine which is neutral or slightly acid to litmus will become slightly alkaline on boiling. None of the conditions have arisen in which a slightly alkaline urine becomes acid on boiling except where ammoniacal fermentation has occurred. The duration of the persistence of the alkaline reaction has also been noted.

An exact regulation of some of the minor conditions which affect the reaction of the urine was not attempted inasmuch as it seems preferable to establish a normal standard which at least would be beyond the influence of such factors as the ordinary variations in diet and in water intake. Under certain circumstances the frequency of micturition might influence the reaction. In some of the conditions which have been studied, particularly in uræmia, it is impossible to obtain specimens of urine at any fixed intervals. The one precaution which was observed in pathologic conditions was to obtain urine specimens, when possible, as often as every three or four hours and in all instances to avoid the accumulation in the bladder of excessively large amounts of urine. In a portion of the work a uniform period was adopted, specimens being collected every three hours.

Normal Individuals.—The determinations which have been reported[3] of the tolerance of normal individuals to intravenous injection show that, at least under certain conditions, small amounts of sodium bicarbonate will effect a change in the reaction of the urine. Thus, in eight cases, four individuals received quantities of 4½ to 5 grams and responded promptly with an alkaline urine. In four other cases, receiving smaller amounts, namely, 2 to 3 grams, the results varied: in two of these individuals the urine became alkaline, but in the other two it remained acid.

In order to extend these data an additional series of cases has been tested with the purpose of determining the efficiency of ingestion methods. In the selection of individuals, normal adult males were chosen. These men were living on an ordinary mixed diet and, for the most part, they were taking but little exercise. While this represents the standard conditions under which one would expect to carry out tests on pathologic cases, yet in the interpretation of data it would be more satisfactory to know the maximum quantities of sodium bicarbonate that would be just sufficient to bring about an alkaline reaction of the urine under any conditions that could be regarded as essentially normal. Perhaps the highest quantities might be required in men who are performing heavy labor and taking an abundant meat diet. While we have no data for this class, still some evidence has been obtained which has some bearing on the maximum values that might be expected. Since under normal conditions certain individuals may excrete an alkaline urine, it has seemed sufficient for the present purposes to determine only the maximum values that may be required.

The question of the proportion between the weight of the individual and the dosage of bicarbonate is not a simple one. If an increase in weight involved a proportional increase in each of the important constitutents of the body, more especially the water, protein and fat, then calculations of dosage per kilo of body weight would be desirable. However, if the increased weight of an individual under consideration is due to an increase, for example, of fat alone, then the comparison of individuals might be more accurate than the regulation of the dosage in proportion to the body weight. Accordingly, in the absence of an exact basis on which to proceed, constant quantities of bicarbonate have been used and the weight of the individual has been recorded.

The first group of cases in Table I gives the preliminary results, showing the effect of the ingestion of 5 grams of sodium bicarbonate. Only those individuals were tested whose urine was distinctly acid to litmus. Specimens of urine were not collected at fixed intervals. In some instances several repetitions of the test were made in the same individual.

TABLE I.

SHOWING THE EFFECT OF THE INGESTION OF 5 GRAMS OF SODIUM BICARBONATE ON THE REACTION OF THE URINE IN NORMAL INDIVIDUALS.

Individual.	Interval between tests.	Weight (lbs.).	Reaction of urine before ingestion of bicarbonate.	Interval between specimens (hrs.).	Reaction to litmus.	Interval between specimens (hrs.).	Reaction to litmus.	Interval between specimens (hrs.).	Reaction to litmus.	Interval between specimens (hrs.).	Reaction to litmus.	Duration of change in reaction (hrs.).
A	....	180	Ac.	4½	Alk.	3½	Ac.	..	....	..	....	4½
	2 days	..	Ac.	4½	Amphot.	3	Amphot.	3	Ac.	..	....	7½
	7 days	..	Ac.	2	Alk.	7½	Ac.	..	....	..	....	2
	6 wks.	..	Ac.	3	Alk.	6	Alk.	2	Ac.	..	....	9
B	....	130	Ac.	2	Alk.	2	Ac.	2	Alk.	1½	*Neut.	..
	3 days	..	Ac.	4	Ac.	2	Ac.	2	Alk.	1½	Ac.	2
	4 days	..	Ac.	2	Alk.	2	Alk.	3	Ac.	..	....	4
	25 days	..	Ac.	3	Alk.	3	Ac.	2	Amphot.	3	Ac.	3
C	....	130	Ac.	3	Alk.	3	Ac.	..	....	..	...	3
	7 days	..	Ac.	3	Alk.	3	Ac.	..	....	..	....	3
D	....	125	Ac.	2½	Ac.	3½	Amphot.	3½	Neut.	2	*Neut.	9
E	....	150	Ac.	3½	Alk.	3	Alk.	2	Alk.	2	Ac.	8½
F	....	155	Ac.	Alk. for 10 hrs.		....		..	....	..	....	10

*The succeeding specimen was acid.

In an additional group the ammonia coefficient was determined and the degree of acidity of the urine was estimated in order to insure the selection of some cases in which the acid metabolism approached the maximum values which occur under normal conditions. In this group the urine was collected, as far as possible, at intervals of three hours.

[3] Sellards: Philippine J. Sc., B. Manila, 1910, V, 363; Sellards and Shaklee: Ibid., 1911, VI, 53.

TABLE I—CONTINUED.

Individual.	Weight (lbs.).	Character of urine before administration of bicarbonate.			Sodium bicarbonate, grams.	Reaction of urine after bicarbonate.		Repetition of sodium bicarbonate, grams.†	Reaction of urine after bicarbonate.		Duration of change in reaction.
		Litmus.	Acidity.*	Ammonia coefficient.		3 hours.	6 hours.		9 hours.‡	12 hours.‡	
A	180	Ac.	6.0	4.4%	5	Alk.	Alk.	0	Ac.	Ac.	6
B	130	Ac.	3.7	4.1%	5	Alk.	Ac.	0	....	....	3
D	125	Ac.	3.0	3.8%	5	Ac.	Alk.	0	Alk.	Ac.	6
F	155	Ac.	1.2	5.9%	5	Ac.	Alk.	0	Ac.	....	3
G	135	Ac.	3.5	5.1%	5	§ Very faintly ac.	Ac.	0	Ac.	Ac.	..
G	...	Ac.	3.5	4.4%	5	Alk.	Ac.	0	Ac.	Ac.	3
H	110	Ac.	3.6	4.4%	5	Alk.	Ac.	0	Ac.	Ac.	3
I	140	Ac.	2.8	4.0%	5	Ac.	Ac.	5	Alk.	18 hrs.	18
J	150	Ac.	3.3	5.3%	5	Ac.	Ac.	5	Alk.	Ac.	3

* Per cent of N/1 solution (titrated with phenolphthalein).
† Six hours after the first administration.
‡ That is, after the first administration of bicarbonate.
§ Well-marked precipitate of phosphates on boiling.
‖ Repetition after 5-day interval.

Certain minor differences were noted in regard to the manner in which the various cases reacted. In many instances the reaction changed suddenly from acid to alkaline and then returned promptly to a definitely acid reaction. In others the change was much slower, the reaction gradually becoming neutral or slightly alkaline, and then returning first to a faintly acid, and eventually to a distinctly acid reaction. In one instance (Individual B) there was a distinct tendency, after the administration of bicarbonate, for the urine to fluctuate between a faintly acid and a faintly alkaline reaction. This case, however, constituted an exception, the rule being that the acid reaction would persist after it had once returned.

Another point which is of especial importance in connection with the testing of pathologic cases is the interval of time which is required for the bicarbonate to take effect. In the series of intravenous tests, which were referred to, the alkaline reaction frequently made its appearance at an early period, sometimes within one hour after injection. In the preceding ingestion tests an alkaline reaction often appeared after an interval of three hours. In subsequent work with cases which showed an increase in tolerance, it was considered permissible to repeat the bicarbonate after an interval of six hours and in some instances small doses were repeated at intervals of three hours. This increases the danger of exceeding the minimal quantity which might be required, but this can be partially controlled by observing the length of time that the alkaline reaction persists.

From the data in Table I it is seen that although the ingestion of 5 grams of sodium bicarbonate in one dose was not always sufficient to bring about an alkaline reaction of the urine, yet it usually produced a definite and readily appreciable effect, the reaction changing, for instance, from a distinctly acid to a neutral or faintly acid reaction with precipitation of phosphates on boiling. The two cases in which no effect was produced were neurotic men who were taking limited amounts of fluid and were excreting small quantities of urine, the rate being as low as 25 cc. for periods of three hours. After an interval of six hours the 5 gram quantity was repeated and both individuals responded promptly with an alkaline urine.

After considering the preceding data it seemed desirable to determine whether or not one might find any individuals who would fail to excrete bicarbonate in the urine after the ingestion of 10 grams at one dose. This amount is so much in excess of the quantity which is required in the majority of instances that it would seem best to select individuals who would probably require larger amounts than are ordinarily necessary. Instead of looking for cases in which the acid metabolism had spontaneously reached the upper limits of normal, it seemed feasible to produce a slight increase in the normal degree of acidosis. The data in the following outline are compiled from subsequent tables showing the behavior of individuals toward 10 grams of sodium bicarbonate after two days of carbohydrate free diet.

INGESTION OF 10 GRAMS OF SODIUM BICARBONATE AFTER TWO DAYS OF CARBOHYDRATE FREE DIET.

Reaction of urine.	Total acetone (grams per day).	β-oxybutyric acid (grams per day).	Effect on the reaction of the urine.
Ac.	0.602	2.374	Amphot. 9 hrs.
Ac.	0.282	0.184	Amphot. 3 hrs.
Ac.	0.621	1.111	Neut. 3 hrs.

In all of these cases a distinct effect was produced upon the reaction of the urine. It would seem a little unexpected if spontaneous fluctuations in diet could produce as much change as that resulting from two days of carbohydrate free diet.

TOLERANCE TO SODIUM BICARBONATE IN ACIDOSIS.

The next step which was undertaken was the study of the behavior of the body in a state of acidosis to the introduction of sodium bicarbonate. In order to compare this behavior with the usual signs of acidosis it seemed desirable to work with acidoses produced artificially rather than those occurring spontaneously. For purposes of study the production of an artificial acidosis possesses several advantages. The exact cause of the acidosis and the degree to which it extends is under control. Furthermore, before the production of the acidosis, one can determine the normal condition of the individual under consideration.

It might appear *a priori* that the introduction of bicarbonate into the body would serve for the detection of acidosis only in comparatively advanced conditions. In considering the degree of delicacy which one might expect from such a procedure it may be well to consider the usual course of events in an acidosis. It is generally accepted that, even in the terminal stages of diabetic acidosis, no free acid exists in the fluids of the body which are in general circulation, *i. e.*, the acid produced in the tissues has not only been neutralized, but,

at least, a slight excess of base predominates and the blood retains an alkaline reaction. Consequently, upon the introduction of bases into the body, the hydroxyl ions do not meet with free hydrogen ions and instead of neutralizing acids immediately the bases are taken up by the tissues in order to replace those which have been previously removed by acid.

It would seem, therefore, that the delicacy of the method in question would depend essentially, in the first place, upon the promptness with which the tissues give up their fixed bases when the acid metabolism increases, and secondly upon their capacity for binding sodium bicarbonate when it is presented to them. One important question which suggests itself is whether the introduction of comparatively large amounts of bicarbonate, either directly into the blood stream or through the alimentary tract, might not result in a temporary overwhelming of the kidney with bicarbonate, resulting in its excretion in the urine before the tissues could make good any deficiency which they might have suffered.

Routine.—For the production of acidosis, carbohydrate starvation was used as the principal method, though some preliminary tests were carried out in which mineral acid was introduced into the body without any alteration in the diet.

The signs of acidosis which were observed in the starvation cases were as follows:

1. Titration of the degree of acidity of the urine by Folin's[4] method.

2. Estimation of the total acetone and the β-oxybutyric acid by Shaffer's[5] method. (The total acetone includes both the preformed acetone and the acetoacetic acid.)

3. Determination of the ammonia coefficient.

4. Determination of the tolerance to sodium bicarbonate.

Analyses of the blood for alkalinity or carbon dioxide content were not made, inasmuch as no well-developed grades of acidosis were produced.

These tests were first carried out while the individual was on an ordinary mixed diet. Then a carbohydrate free diet was maintained, usually for a period of two days, and on the third day the tests were repeated, the carbohydrate free diet being maintained until the completion of the tests. Ordinarily the determination of the tolerance to sodium bicarbonate did not occupy an entire day. In Table II the figures given in parenthesis for the final day of each test represent the calculated values for a 24-hour period; these calculations are based on the data obtained for the fraction of the 24 hours during which the observations were made. On account of the necessity of introducing this calculation, the quantities per liter have been recorded as well as the quantities per day.

After a few determinations it was found that the response to the carbohydrate free diet, in most instances, was not sufficiently great to effect an increase in the ammonia coefficient. The general behavior of the ammonia coefficient is recorded in the first two cases in Table II (A and D). In the majority of the remainder of the cases the degree of acidosis did not appear to be sufficient to warrant the determination of the ammonia nitrogen. The titration of the degree of acidity of the urine did not show significant changes except in one instance, where the acidity was unusually low at the beginning of the period of carbohydrate free diet. These data were not of sufficient interest to be included in the tables.

In all instances the sodium bicarbonate was given by ingestion. One important point on which information was desired was the manner of estimating the dosage of bicarbonate in unknown conditions. In those cases in which there is no guide concerning the quantity which will be required, the most feasible procedure consists in starting with an amount which can be readily borne by a normal individual. This quantity may then be repeated or even increased according to the behavior of the individual in question. The behavior of the normal individuals recorded in Table I was taken as a guide in determining the interval of time at which a repetition should be made. The maximum interval which has been used in the ingestion tests is six hours. In some instances an interval of three hours has been used and this seems to involve comparatively little danger in overstepping the amount of bicarbonate which is required.

In addition to the carbohydrate starvation cases, some preliminary observations were made on the effect of the ingestion of mineral acids. In two cases dilute hydrochloric acid was used in quantities of 2 cc. three times per day for four and five days. The absolute quantities for the total period were

TABLE II.

SHOWING THE TOLERANCE TO SODIUM BICARBONATE AFTER ONE TO THREE DAYS OF CARBOHYDRATE FREE DIET, TESTED BY THE INGESTION OF 5 GRAMS OF SODIUM BICARBONATE EVERY SIX HOURS.

Individual.	Day.	Diet.	Ammonia coefficient.	Total acetone (grams).		β-oxybutyric acid (grams).		Tolerance to sodium bicarbonate.	
				Per liter.	Per day.	Per liter.	Per day.	Gms.	Effect on urine.
A	1	Mixed.	2.7	0.010	0.015	0.057	0.084		
	2	Do.	2.2	0.010	0.014	0.067	0.094	5	Alk. 6 hrs.
	3	Do.	2.5	0.012	0.010	0.110	0.090	..	
	4	Do.	3.1	0.017	0.015	0.081	0.073	..	
	5	Carbohydrate free.	3.3	0.144	0.106	0.139	0.103	..	
	6	Do.	*1.9	0.329	(0.230)	0.249	(0.174)	10	Alk. 3 hrs.
D	1	Mixed.	....	.....	.....	.....	.....	5	Alk. 3 hrs.
	2	Do.	3.8	0.010	0.011	0.053	0.062	..	Neut. 3 hrs.
	3	Carbohydrate free.	2.7	0.018	0.027	0.086	0.127	..	
	4	Do.	2.4	0.230	0.161	0.381	0.267		
	5	Do.	*1.9	0.758	0.856	1.705	1.927	25	Alk. 6 hrs.
G	1	Mixed.	....	.....	.....	.....	.....	5	Faintly ac.
	2	Carbohydrate free.	....	0.027	0.054	0.00	0.00	..	
	3	Do.	....	0.031	0.036	0.080	0.092		
	4	Do.	....	0.028	(0.049)	0.054	(0.094)	15	Alk. 6 hrs.
H	1	Mixed.	....	.....	.....	.....	.....	5	Alk. 12 hrs.
	2	Carbohydrate free.	....	0.032	0.035	0.035	0.038	..	
	3	Do.	....	0.083	0.079	0.130	0.123	..	Neut. 3 hrs.
	4	Do.	....	0.188	(0.263)	0.142	(0.200)	5	Alk. 3 hrs.
K	1	Mixed.	....	.....	.....	.....	.....	5	Alk. 3 hrs.
	2	Carbohydrate free.	....	0.023	0.040	0.042	0.074	..	
	3	Do.	....	0.045	0.074	0.071	0.116	..	Alk. 9 hrs.
	4	Do.	....	0.160	0.272	0.170	0.289	20	Amphot. 3 hrs

* During the administration of bicarbonate.

[4] Folin: Am. J. Physiol., Bost., 1903, IX, 265.

[5] Shaffer: J. Biol. Chem., Balt., 1908, V, 211.

TABLE II—CONTINUED.

SHOWING TOLERANCE TO SODIUM BICARBONATE ON THE THIRD DAY OF CARBOHYDRATE FREE DIET.

(1) INGESTION OF 10 GRAMS SODIUM BICARBONATE IN ONE QUANTITY.

Individual.	Day.	Diet.	Total acetone (grams).		β-oxybutyric acid (grams).		Tolerance to sodium bicarbonate.	
			Per liter.	Per day.	Per liter.	Per day.	Gms.	Effect on urine.
F	1	Mixed.	.....	.....	.....	.....	5	Alk. 12 hrs.
	2	Carbohydrate free.	0.011	0.010	0.036	0.032	..	
	3	Do.	0.015	0.025	0.038	0.065	..	
	4	Do.	0.322	(0.692)	1.104	(2.374)	10	Amphot. 9 hrs.
H	1	Mixed.	.....	.....	.....	.....	5	Alk. 3 hrs.
	2	Carbohydrate free.	0.032	0.035	0.035	0.038	..	
	3	Do.	0.083	0.079	0.130	0.123	..	
	4	Do.	0.188	(0.282)	0.142	(0.184)	10	Amphot. 3 hrs.
L	1	Mixed.	.....	.....	.....	.....	5	Alk. 3 hrs.
	2	Carbohydrate free.	0.383	0.254	0.634	0.444	..	
	3	Do.	0.298	0.620	0.363	0.755	..	
	4	Do.	0.414	(0.621)	0.741	(1.111)	10	Neut. 3 hrs.
(2) INGESTION OF 5 GRAMS SODIUM BICARBONATE EVERY 3 HRS.								
I	1	Mixed.	.....	.....	.....	.....	*10	Alk. 18 hrs.
	2	Carbohydrate free.	0.054	0.054	0.073	0.073	..	
	3	Do.	0.077	0.069	0.240	0.216	..	
	4	Do.	0.255	(0.255)	0.313	(0.313)	10	Very faintly ac. 6 hrs.
J	1	Mixed.	.....	.....	.....	.....	*10	Alk. 3 hrs.
	2	Carbohydrate free.	0.048	0.082	0.087	0.148	..	
	3	Do.	0.064	0.109	0.139	0.236	..	
	4	Do.	0.170	(0.289)	0.257	(0.437)	15	Very faintly ac. 6 hrs.

* Two quantities of 5 grams at intervals of 6 hours.

2.8 and 2.2 grams. As will be seen in the accompanying outline, the rise in tolerance to sodium bicarbonate was perhaps even slightly greater than could be accounted for by the bases which this amount of acid could withdraw, 2.8 grams hydrochloric acid corresponding to 6½ grams, and 2.2 grams to 5 grams of sodium bicarbonate. In the third case about half of this quantity of acid was used and, as would be expected theoretically, no rise in tolerance occurred.

TABLE III.

SHOWING THE TOLERANCE TO SODIUM BICARBONATE AFTER THE INGESTION OF HYDROCHLORIC ACID.

Individual.	Day.	Acidity of urine.*	Ammonia coefficient.	Ingestion of hydrochloric acid.	Tolerance to sodium bicarbonate.†	
					Gms.	Effect on reaction of urine.
L	1	1.4	5.9	None.	5	Alk. 6 hrs.
	7	2.3	5.8	2.8 grams in 5 days.	‡15	Reaction reduced to slightly acid for 3 hrs.
M	1	1.5	5.0	None.	5	Alk. 3 hrs.
	6	2.6	5.4	2.2 grams in 4 days.	‡15	Alk. 3 hrs.
N	1	...	...	None.	5	Alk. 3 hrs.
	6	...	...	1.2 grams in 4 days.	10	Alk. 15 hrs.

* Per cent N/1 solution (titrated against phenolphthalein).
† Second test was made 15 hours after the last administration of hydrochloric acid.
‡ 10 grams at the first dose and 5 grams 6 hours later.

This series was not extended any further inasmuch as the ingestion of hydrochloric acid is not very well borne and these controls are not altogether essential.

The data for the tolerance tests in Table II would, in many instances, be without significance except for the fact that the normal, for the individual under consideration, had been determined only a few days before. Under these circumstances the conclusion would seem to be justified that the tolerance to sodium bicarbonate begins to rise very early in the course of an acidosis. This would indicate that an increased production of acid was met in part by the fixed bases of the tissues and not wholly by an interception of ammonia and by the excretion of acid salts. Observations which are related to these data have been made upon the ammonia excretion and the acidity of the urine after the ingestion of food containing an excess of acid forming elements. After the ingestion of the equivalent of as much as 32.7 cc. normal acid per day, Sherman and Gettler[3] found that the increase in the output of ammonia and acid salts in the urine was sufficient to account for only about three-fourths of the ingested acid. However, they do not attribute the neutralization of the remainder to the fixed bases.

Of the three procedures used in Table II for the administration of the bicarbonate, it would seem that the ingestion of 5 grams every six hours constituted the most delicate test. A further control for this manner of administration might have been carried out, repeating the quantities of 5 grams every six hours on normal individuals. However, where the individual reacts to the first ingestion of 5 grams, it would seem superfluous to repeat this after six hours.

Naturally there is no mathematical proportion between the tolerance to sodium bicarbonate and these small quantities of acetone and oxybutyric acid which were obtained after two or three days of carbohydrate starvation. However, in the spontaneous acidoses of high grade which occur in diabetes, it would appear that, in general, when the quantities of β-oxybutyric acid are high, the body will take up proportionally large amounts of carbonates. The exact relationship of these two factors does not appear to have been studied closely, but apparently there are no exceptions to the general parallelism.

The tolerance tests are certainly not as simple as the determination of acetone for the detection of slight grades of acidosis in well-known conditions, such as starvation. Their advantage would appear to lie in the possibility of their application in some of the clinical conditions in which acidosis is suspected but in which definite evidence is lacking.

An opportunity does not ordinarily present itself for the determination of the order in which the various signs of acidosis appear. A general classification can be made, however, by observing the signs which are found in various stages of acidosis.

Among the earliest signs of starvation are the appearance of acetone and an increase in the acidity of the urine.

This is followed very closely by the appearance of acetoacetic and β-oxybutric acid and, presumably, by the neu-

[3] Sherman and Gettler: J. Biol. Chem., Balt., 1912, XI, 323.

tralization and excretion of the fixed bases and a rise in the tolerance to bases.

The exact position of the ammonia coefficient is a little hard to determine. While its increase may begin rather early, nevertheless, it does not reach a point which is definitely abnormal until the preceding signs are fairly well marked.

The most prominent of the later changes are the diminished alkalinity of the blood as determined by titration, its decreased carbon dioxide content and the development of air hunger.

Pathologic Conditions.—In the selection of pathologic material for study, those conditions were chosen in which an acidosis, due to other than β-oxybutyric acid, may be suspected. Especial attention was given to some of the different types of nephropathies. Diabetic cases of a certain type were also studied. It will be remembered that Naunyn has emphasized the possibility of the occurrence of other acids in addition to β-oxybutyric in diabetes. We have sought for such evidence by applying the tests for tolerance to sodium bicarbonate in suitable cases.

One case representing an obscure toxæmia of pregnancy is also discussed, since it illustrates certain theoretical considerations in connection with acidosis.

Diabetes.—In looking for evidence of acids which do not commonly occur in diabetes, patients were selected in whom the urine did not show acetone and acetoacetic acid. Three were studied who were excreting sugar freely when on a mixed diet and two others who showed an intermittent glycosuria. The general results are shown in Table IV.

TABLE IV.

SHOWING THE BEHAVIOR OF THE EARLIER STAGES OF DIABETES TOWARD SODIUM BICARBONATE.

Case No.	Weight (lbs.).	Sugar excretion on mixed diet (grams per day).	Tolerance to carbohydrate (grams white bread per day).	Acidity in % of N/1 solution.	Ammonia coefficient.	Total acetone (grams per day).	β-oxybutyric acid (grams per day).	White bread in diet (grams per day).	Sugar excretion (grams per day).	Tolerance to sodium bicarbonate.	
										Grams.	Effect on urine.
1	130	35	175	5.3	5.6	0.011	0.014	150	0	40 in 30 hrs.	Alk. 9 hrs.
2	110	(*)	(*)	3.0	2.6	0.023	0.061	170	0	30 in 30 hrs.†	Alk. 12 hrs.
3	140	120	100	3.6	5.8	0.085	0.259	200	26	10 in one injection.	Alk. 9 hrs.
4	145	25	100	6.3	6.4	0.010	0.083	(§)	25	30 in 12 hrs.‡	Faintly ac. 3 hrs.

* Intermittent glycosuria.
† By ingestion 5 grams every 6 hrs.
‡ By ingestion 10 grams every 6 hrs.
§ Mixed diet.

In addition to the cases in Table IV, a fifth patient, showing intermittent glycosuria, was tested at a time when the urine was free from acetone and sugar. The ingestion of 10 grams of sodium bicarbonate in one quantity brought about an alkaline reaction of the urine which persisted for 15 hours.

Of the four cases in the preceding table it is seen that none of them exhibited definite signs of acidosis as tested by the ordinary methods. In regard to the tolerance for sodium bicarbonate the third case showed no definite increase. The conditions under which the second case was tested suggest at least a slight increase above the normal, but this case was complicated by a heart lesion of sufficient extent to contraindicate any intravenous work. The first and fourth cases afford proof of a distinct increase. Subsequent examinations were carried out in order to determine whether the results would be consistent on repetition. The results were as follows:

The second patient after an interval of 18 days was given 5 grams of sodium bicarbonate by mouth every 2 hours. Twenty-five grams were required to bring about an alkaline reaction of the urine.

In the third patient, after an interval of 10 days, the ingestion of 10 grams of sodium bicarbonate in one quantity brought about an alkaline reaction of the urine which persisted for 6 hours. After another interval of 10 days, 5 grams of sodium bicarbonate was given by mouth every three hours. After the administration of 10 grams the urine became faintly alkaline for 3 hours.

The test was not repeated in the fourth patient. In the first patient several repetitions were made by intravenous injections. The results are shown in the following outline.

REPETITIONS OF THE INTRAVENOUS INJECTIONS OF BICARBONATE IN CASE I.

Interval between tests.	Ammonia coefficient	Total acetone (grams per day).	β-oxybutyric acid (grams per day).	Tolerance to sodium bicarbonate.	
				Grams.	Effect on urine.
....	5.6	0.011	0.014	40 in 30 hrs.	Alk. 9 hrs.
8 days	6.0	0.010	0.050	40 in 30 hrs.	Alk. 8 hrs.
5 days	5.7	0.018	0.041	30 in 18 hrs.	Alk. 7 hrs.

These data show that the results in Table IV, as far as they have been tested, were consistent on repetition. The behavior of the first and fourth cases was rather unexpected. These two patients had noticed symptoms over a period of several years; it might be supposed that their abnormal reaction toward sodium bicarbonate had required a relatively long period for its development and that perhaps this condition would return only after a long interval. The preceding outline, however, shows that, at least in the first case, a few days were sufficient to permit its return.

A comparison of these two cases (Nos. 1 and 4) showing an increase in tolerance with the one (No. 3) whose tolerance is normal is somewhat instructive. Here we have three men, in a similar stage of diabetes. None of them represents the adipose type of the disease. All excrete sugar freely but become sugar free when the carbohydrate intake is moderately reduced. No definite signs of acidosis are present, the excretion of acetone being normal, and the ammonia not being significantly increased. Yet, their behavior toward sodium bicarbonate is radically different. The only indication of this difference consists in the subjective symptoms of which these men complained. The two who showed a well-marked in-

crease in tolerance toward bicarbonate had developed symptoms referable to the nervous system. The first one came to the hospital asking for treatment for symptoms of ataxia,[7] and the other for symptoms indicating an early multiple neuritis. The third case showed no signs of any involvement of the nervous system and complained primarily of the usual symptoms referable to starvation and glycosuria, but he also spoke of pains in the legs and muscles.

In the course of a year only two cases of this first type have been observed. It will prove of more interest and importance if this condition is fairly common, rather than if it is an unusual occurrence. In considering its explanation it is important to note that no signs of nephritis were present. Otherwise one might think of the possibility of the retention of bicarbonate on account of defective kidney function. If one assumes that some unknown acid is responsible for this behavior, then it would seem that the disproportion is rather great between the production of ammonia and the behavior toward the bicarbonate.

Certain other considerations arise which are of theoretical interest. The data in Table I indicate that under normal conditions the body contains almost the maximum amount of fixed bases which it is capable of assimilating, *i. e.*, even when small amounts are presented to it by injection, or by way of the alimentary tract fixed bases promptly appear in the urine. One may inquire, therefore, as to the total quantity of the reserve supply of fixed bases which the body possesses and the extent to which this supply may be depleted before symptoms appear. It is certain that well-marked degrees of acidosis frequently develop without the appearance of definite subjective symptoms. Nevertheless, the replacement of these bases is such a simple matter that it would seem to be a desirable step. In the two patients under consideration it would seem that a deficiency of bases existed, in moderate degree, and under conditions in which it would not be detected by the tests on which one ordinarily relies.

Toxæmia of Pregnancy.[8]—The tolerance exhibited by the cases of diabetes is of especial interest when compared with the results obtained in an obscure toxæmia of pregnancy. The essential features were as follows:

In the third month of pregnancy, pernicious vomiting developed. The ammonia coefficient was high, varying usually from 30 to 35 per cent and these values persisted notwithstanding the introduction of glucose by rectum. A hysterotomy was performed promptly, but without any permanent improvement in the general condition of the patient. On the day following the operation the ammonia coefficient fell from 34.5 per cent to 22.1 per cent, but rose rapidly, eventually reaching 40 per cent. Little food was retained by mouth, but quantities of 75 to 100 grams of glucose per day were given by rectum and the absorption was apparently good. Qualitative tests showed the presence of acetone in the urine. The tolerance to sodium bicarbonate was tested and quantitative estimations were made of the total acetone and β-oxybutyric acid, in order to obtain evidence of the extent of any starvation acidosis which might be present. These tests were made one week after operation. The results were as follows:

INTRAVENOUS INJECTION OF 6 GRAMS OF SODIUM BICARBONATE.

Interval between tests.	Acidity of urine.*	Ammonia coefficient	Total acetone (grams per liter).†	β-oxybutyric acid (grams per liter).†	Effect on reaction of urine.
....	2.5	32.2	0.248	0.021	Alk. or neut. 42 hrs.
2 weeks	2.0	30.0	.....	.....	Alk. 6 hrs.
1 day	1.5	31.9	0.096	0.162	Alk. or neut. 42 hrs.

* Per cent of normal solution.
† The absolute values are not available on account of some incontinence. There was a free excretion of urine however; the daily quantities averaged about 1½ to 2 liters. The absolute quantities of ammonia were not greatly increased, the values varying from 0.6 to 1.4 grams per liter.

The values for β-oxybutyric acid fall within the normal limits of Shaffer's method. The increase in the ammonia coefficient is many times greater than could be accounted for by the slight increase in acetone. The tolerance to sodium bicarbonate is normal. This is in marked contrast to the diabetic patients who showed a normal amount of acetone and no significant increase in ammonia, but a high tolerance to sodium bicarbonate.

There are two factors which might have a bearing on this seeming paradox. In the diabetic cases one must consider the possibility of the occurrence of an unknown acid which had withdrawn fixed bases from the body.

The most plausible explanation of the data obtained in the toxæmic case is that the condition was not a starvation acidosis, but was essentially a primary disturbance of protein metabolism. Theoretically, therefore, the tolerance to sodium bicarbonate in this case would not be increased even though acetone, acetoacetate and β-oxybutyrate were being excreted freely, since the increase in ammonia production was proportionally much greater than the quantities of acid which were produced. The essential feature which this case illustrates is that an increase in the excretion of ammonia and of acetone and its related bodies does not necessarily indicate a disturbance in the equilibrium between acids and bases and it is not always accompanied by a rise in tolerance to sodium bicarbonate.

Nephropathies.—The study of renal diseases in connection with acidosis is of interest from two standpoints. In the first place one must consider whether any of the various nephropathies may interfere with the excretion of substances by which acidosis is ordinarily recognized, and whether in the use of sodium bicarbonate one might find retention of this salt on account of disturbance of the kidney function. On the other hand, the conception has frequently been advanced that nephritis and especially uræmia may be essentially an acidosis. Various findings have been noted which lend more

[7] A definite Romberg sign was not present and the Wassermann and luetin reactions were negative.

[8] I take pleasure in acknowledging the kindness of Dr. J. W. Williams for the privilege of following this case which occurred in the obstetrical service of this hospital. I am also indebted to his staff for many favors and especially for the data on the ammonia metabolism.

or less support to this view. Many observers report a reduction in the alkalinity of the blood. β-oxybutric and other organic acids have been found in the urine. Recently Straub and Schlayer[9] have reported a diminution in the carbon dioxide content of the alveolar air. Senator has been especially prominent among those who have laid emphasis on the possible relation between acidosis and uræmia. von Noorden, however, considers that, although a slight grade of acidosis may be present in uræmia, it represents merely an effect and not the underlying cause of the condition. The consensus of opinion is in agreement with this latter view.

In the application of the sodium bicarbonate tests, in the presence of kidney lesions, the first step evidently consisted in the determination of whether any of the various nephropathies behaved in an abnormal manner toward the introduction of sodium bicarbonate into the body.

In the adoption of a routine for the examination of kidney cases it seemed especially important to carry out the ordinary tests for the detection of acidosis. For this purpose I have depended principally upon the ammonia coefficient and the determination of acetone and oxybutric acid. These two latter examinations seemed necessary in order to control the possibility of a starvation acidosis and also on account of the occasional occurrence of these substances in uræmia.

In addition the test of renal function by phenolsulphonephthalein is also recorded.[10]

No patients were chosen in whom cardio-renal conditions existed, except those in which the cardiac lesion was well compensated and the question of a stasis kidney could be eliminated. For the most part fairly simple cases were selected which corresponded more or less definitely to certain general types of renal lesions. In view of the confusion which exists in the transition from the older ideas to the newer views regarding renal disease it has been difficult to adopt a satisfactory terminology. For example, there is considerable uncertainty as to whether chronic interstitial nephritis is really an inflammatory process and for this reason the more general term "nephropathy" has been used in this paper. In many of the cases which were studied there was evidence of a diffuse involvement of the kidney. Those in which the signs of glomerular lesions predominated are classified in the parenchymatous group while the arteriosclerotic and primarily contracted kidneys are included under the designation of chronic interstitial disease.

The results are given in Table V.

TABLE V.

EFFECT OF SODIUM BICARBONATE ON THE REACTION OF THE URINE IN VARIOUS NEPHROPATHIES.

Case No.	Weight (lbs.).	Type of nephropathy.	Ammonia coefficient (per cent).	Total acetone (grams per day).	β-oxybutyric acid (grams per day).	Administration of sodium bicarbonate.	Reaction of urine to litmus.	Phenolsulphonephthalein output. First hour.	Phenolsulphonephthalein output. Second hour.
						Intravenous injection.			
1	175	Chr. interstitial..	3.6	0.016	0.026	16 gms. in 8 hrs.	Ac.....	24 %	[1]
2	135	Chr. diffuse.....	[2]	0.07 [3]	0.063	40 gms. in 24 hrs.	Ac.[3].....	2 %	5 %
3	170	Acute nephritis with uræmia.	2.0	0.026	0.010	130 gms. in 66 hrs.	Ac.....	[4]	
4	155	Acute exacerbations of chr. parenchymatous.	2.4	0.012	0.076	10 gms. in one injection.	Alk. 24 hrs..	15 %	45 %
5	140	Chr. parenchymatous.	6.4	0.020	0.056	10 gms. in one injection.	Alk. 18 hrs..	5 %	10 %
6	180	Chr. diffuse nephritis with uræmia.	4.4	0.023	0.052	60 gms. in 24 hrs.	Ac.....	Trace.	Trace
7	155	[5]	2.4	0.021	0.022	20 gms. in 20 hrs.	1 alk. specimen.	....	
						Ingestion tests.			
8	130	Chr. diffuse.....	...	0.015	0.055	[6] 10 gms. in 6 hrs.	Alk. 4 hrs...	[7] 30 %	
9	190	Chr. diffuse.....	11.2	0.054	0.045	[8] 30 gms. in 15 hrs.	Ac.....	....	[9]
10	145	Chr. diffuse.....	1.7	0.013	0.030	[8] 30 gms. in 15 hrs.	Ac.....	....	[10]
11	125	Chr. nephritis with diabetes.	6.4	0.006	0.030	[8] 30 gms. in 15 hrs.	Ac.....	17 %	27 %
12	100	Chr. diffuse.....	[2]	.....	.....	[6] 40 gms. in 42 hrs.	Alk. 3 hrs...	Trace.	10 %
13	165	Chr. parenchymatous.	...	.....	.....	5 gms.....	Alk. 6 hrs...	47 %	79 %
14	145	Chr. parenchymatous.	...	.....	.....	[6] 10 gms.....	Alk. 6 hrs...	23 %	45 %

[1] A total of 60 per cent in 3 hrs.
[2] Ammoniacal fermentation in lower urinary tract.
[3] After heating.
[4] A total of 10 per cent in 4 hrs.
[5] Albuminuria in acute rheumatic fever.
[6] 5 grams every 6 hours.
[7] By intravenous injection.
[8] 5 grams every 3 hrs.
[9] A total of 30 per cent in 3 hrs.
[10] A total of 30 per cent in 2 hrs.

Some supplementary data are necessary concerning the more important cases in the preceding table.

Case No. 1. Ten days before this injection this patient received two injections of 10 grams each of sodium bicarbonate in 2 per cent solution with an interval of 8 hours between the injections. The urine remained acid. This result would have been conclusive of an increase in tolerance except for the existence of a slight acetonuria arising from a very restricted milk diet. The urine on the day preceding the injection did not give the qualitative tests for acetone. On the day of the injection the sodium nitroprussid color reaction was suggestive, but the ferric chloride test for acetoacetic acid was negative. Carbohydrates were supplied freely during the interval between the first and second injections. The sodium bicarbonate was used in 2 per cent solution, 500 cc.[11] being introduced at one time. The blood pressure in this patient was high, averaging about 180 mm. of mercury. This quantity of fluid, however, could be introduced, not only without raising the pressure, but it was usually accompanied by a fall of about 30 mm. developing within a few hours and lasting 12 to 18 hours.

Case No. 2. In this patient there was a long standing infection of the lower urinary tract, resulting in ammoniacal fermentation of the urine. In order to determine whether any carbonates were being excreted, samples of urine were concentrated in an evaporating dish over the free flame. When no fixed base was present, the ammonia was soon driven off and the acid reaction of the urine returned. In the same manner, when normal urine is made alkaline with dilute ammonia, the excess of ammonia is driven off on boiling and apparently the ammoniacal salts, formed from the neutrali-

[9] München med. Wochen., 1912, lix, 569.

[10] The writer is indebted to Dr. Rowntree and Dr. Fitz of this university for their kindness in supplying these data from their studies in renal function.

[11] Except in the second injection of the test which is recorded in Table V.

zation of the acid phosphates, are decomposed with loss of ammonia, since the urine becomes not neutral, but acid in reaction. When much fixed base is present, the vapors do not become ammonia free on boiling, on account of the decomposition of urea; however, this does not give rise to any confusion.

These tests were also confirmed by drying and heating litmus paper in the usual manner for distinguishing between ammonia and the fixed bases.

This patient received quantities of 10 grams at each injection in 2 per cent solution. The first injection was followed by a chill with slight rise in temperature accompanied by subjective discomfort. These reactions increased in severity with each injection, and accordingly the bicarbonate was discontinued before any had been excreted in the urine.

Case No. 3. Other important factors in addition to the uræmia were present in this case. The nephritis developed as the result of infarctions from a subacute infective endocarditis. The observations were carried out during a practically afebrile period.[12] This would not be sufficient to exclude a febrile acidosis, inasmuch as this short period had been preceded by a febrile course lasting several weeks. However, if a febrile acidosis did exist, it was of such a type that it could not be detected by the ordinary tests, such as an increase in the ammonia coefficient or the excretion of acetone. A positive Wassermann reaction was obtained, but this was the only evidence of syphilis.

This patient had been under observation in the ward for one week. At the time of the first injection the symptoms of uræmia were fairly definite. None of the usual signs of acidosis were present. There was a gradually increasing dyspnœa. The respirations were moderately deep and free; the rate varied from 28 to 36 per minute. The mucous membranes were bright in color, although the hæmoglobin and the red blood count were low. On one occasion the patient called repeatedly for "air," and when questioned he said that he had no pain, but could not get his breath. There were no physical signs in the lungs at this time to account for this symptom.

Twenty grams of sodium bicarbonate in 2½ per cent solution were given at the first injection. Three injections were made in the next 32 hours. Quantities of 20 and 30 grams were introduced at one time, increasing the concentration to 4 and then to 5 per cent. The respiratory rate fell to 18 and even as low as 14 per minute. At times there was definite Cheyne-Stokes' respiration. Muscular twitchings of the face and the upper extremities also developed. These were not extensive, involving only one or two movements at a time. They persisted intermittently until death, but intervals of several hours frequently occurred in which no twitchings appeared. A localized œdema developed in the left hand. The veins at the elbow on this side had been used repeatedly for injections and withdrawal of blood specimens, but there were no evidences of thrombosis. In the next 24 hours the œdema diminished markedly.

A specimen of blood serum taken after the fourth injection of bicarbonate did not show any increase in the alkalinity as measured by titration with N/10 acid against dimethylamido-azobenzene. An additional injection of 30 grams was given. The injections were then discontinued, inasmuch as the dyspnœa did not return and there was no indication that an alkaline urine could be obtained or that a polyuria could be produced. A distinct oliguria persisted, though anuria did not develop. Death occurred 32 hours later.

The autopsy[13] showed extensive infarction of the kidneys accompanied by an acute diffuse nephritis. Microscopically the involvement of the glomeruli was very general. The interstitial tissue was nowhere increased, but accumulations of mononuclear cells were scattered throughout the renal tissue in greater abundance than normal. The blood vessels were everywhere congested.

Case No. 6. This patient was a chronic nephritic in uræmia. Œdema was well marked, especially over the lower extremities. A satisfactory response was not obtained to any therapeutic measures. Sixty grams of sodium bicarbonate in 24 hours, divided into three injections of 20 grams each, failed to change the reaction of the urine. Titrations made before and after the injections of bicarbonate showed no diminution in the degree of acidity. The œdema was not influenced. Fair quantities of urine were passed until the time of death, which occurred 24 hours after the last injection.

At autopsy the kidneys were found to be slightly enlarged. A chronic diffuse nephritis was present. Microscopical examination showed a uniform increase in fibrous tissue. The glomeruli were large; the uriniferous tubules were atrophic in places while in other areas they were dilated and lined by a low epithelium. The blood vessels showed a slight amount of thickening.

Case No. 7. This case showed a marked grade of albuminuria, accompanying acute rheumatic fever, the urine containing 1 per cent of albumin on the day of injection. No casts were present. This patient was introduced into this series on account of the indefinite significance of albuminuria in nephritis. The tolerance to bicarbonate was definitely increased, but this might be interpreted as evidence of a slight acidosis in rheumatic fever.

Case No. 8. This case was a cardio-renal patient. The test recorded in the table was made at the first appearance of symptoms of uræmia and showed that there was no increase in tolerance to bicarbonate. The nitrogen and water output remained good, but death occurred two weeks later, the symptoms of uræmia persisting.

The autopsy showed a chronic and subacute diffuse nephritis. Microscopically the cortex of the kidney was markedly scarred. The glomeruli were prominent; many of them were converted into hyaline masses while others were larger than normal and very cellular. The tubules were lined by a low cubical epithelium which was coarsely vacuolated and in some places it was granular. The interstitial tissue was increased in patches and in such areas

[12] Blood cultures made by Dr. Major showed that the *Streptococcus viridans* was present in considerable numbers during this period.

[13] The notes upon the autopsy findings in these three cases were furnished very kindly by Dr. Winternitz.

the tubules and glomeruli showed retrogressive changes. The fibrous tissue increase was characterized further by an infiltration of mononuclear cells. The blood vessels showed thickening of their walls in the region of the fibrosed areas but otherwise they were not markedly involved.

Case No. 9. This is the only instance in which a high ammonia coefficient was obtained. A subsequent test five weeks later gave an ammonia coefficient of 9.5 per cent. This is of comparatively little interest, however, since this case was complicated with hepatic cirrhosis.

Case No. 11. This result can hardly be interpreted on account of the coexistence of diabetes and nephritis; the patient at the time of this test was sugar free. The result is perhaps of some negative value to show that the tolerance in this instance was not normal.

The case also serves to illustrate a situation which may arise in the handling of diabetic patients. Thus Naunyn has emphasized that the same sclerosis of the blood vessels which gives rise to changes in the pancreas may also involve the kidney and affect the renal function. In this manner the occurrence of diabetes and nephritis in the same individual gives rise to two conditions either of which may increase the tolerance to bases. In diabetic coma it is assumed that the administration of carbonates should be continued until they appear in the urine. However, the same rule is not yet established for the nephropathies. Consequently in an uncomplicated case of diabetic coma the explanation of the persistence of an acid reaction of the urine after the introduction of carbonates may be essentially different from a similar case in which renal lesions are present.

The intravenous injection of bicarbonates in many of the preceding cases was not well borne. Reactions frequently appeared which were similar to those known as "salt fever," following the intravenous injection of physiological salt solution. These reactions were especially pronounced in the two cases of chronic parenchymatous nephritis. The stimulating effect of sodium bicarbonate[14] was observed in some instances. The reactions were severe enough to contraindicate the intravenous injection of bicarbonate except in selected cases. On account of these reactions and in the absence of the explanation of this increase in tolerance, it seemed sufficient to establish whether the tolerance was normal or distinctly increased without attempting to determine the maximum limits of this increase. The two patients (Nos. 3 and 6) who received the largest quantities developed no reaction and experienced no discomfort, except for some stimulating effect seen in the second case (No. 6). Also no disturbances were observed in the ingestion tests following the quantities of bicarbonate which were used.

One feature which seems remarkable is that such large quantities of salt could be introduced in advanced cases of nephritis without any definite influence on the œdema. Though many of the observations in œdema have been made with sodium chloride yet since the effect of the salt is supposedly due to salt action *per se* and not to any specific properties of the ions themselves, the sodium bicarbonate should be only moderately less effective than the sodium chloride.

The one feature which is most prominent in Table V is that a distinct difference exists in the excretion of the carbonates in various types of nephropathy.

In the four cases of the chronic parenchymatous type sodium bicarbonate is readily excreted. This agrees with von Noorden's statement that carbonates are readily excreted in nephritis. Furthermore, the cases which behave in this manner do not support Fischer's[15] views regarding acidosis in nephritis. Indeed the data from the control cases would enable one to exclude acidosis rigidly in these four cases of chronic parenchymatous nephritis except for the theoretical possibility that even in acidosis the parenchymatous nephritic kidney would permit the excretion of bicarbonates under conditions in which, with a normal kidney, the bicarbonates would be retained by the tissues.[16]

In some of the cases, however, there was a noteworthy increase in the amount of bicarbonate which could be administered without affecting the reaction of the urine. There is but one case (No. 6) in which we have a pure nephritis which is free from infections or other complicating factors, and in which we have clear proof of a well-marked increase in tolerance, as tested by intravenous injections. Nevertheless the general behavior of the cases indicates that there are several diverse conditions among the nephropathies in which an increased tolerance may be expected. In addition to the diffuse nephritides, an impression was gained that the arteriosclerotic changes in the kidney were especially likely to give rise to an increase in tolerance. Prominent among the conditions which give a high tolerance are the acute nephritides with typical uræmia. The results of the tolerance tests in the uræmia appearing in Asiatic cholera show a very definite increase. In the present series, the uræmia developing in the course of an infective endocarditis (Case No. 3) would indicate that these results are not specific for Asiatic cholera, but that they occur in other infections. Similarly, the behavior of the case of uræmia which was free from infection (Case No. 6) would likewise indicate that such results were not specific for bacterial infections, but that they occur in other toxæmias.

In the group of nephropathies which show an increase in tolerance to bases the possibility of an acidosis cannot, as yet, be excluded. At present we have gone no further than to attempt to establish the existence of this condition and have not

[14] Dawson: J. Exper. M., N. Y., 1905, VII. 1.

[15] Fischer, Martin H.: Nephritis. 1912. John Wiley & Sons. New York.

[16] Another suggestion may be offered in support of Fischer's hypothesis. The term acidosis, in its accepted sense, has come to mean a more or less general depletion in the available supply of bases in the body. However, it is conceivable that a condition of a very different nature might be brought about by a localized accumulation of free acid in the kidney, for example, resulting in lesions due to the direct action of the acid on the protoplasm of the cells. The plausibility of such an occurrence might be argued from the supposed susceptibility of the kidney to acids and from its functional activity in the excretion of acids in order to spare the other tissues of the body.

yet investigated its explanation. It does not necessarily follow that the injected bicarbonate is retained in the system. With the impairment of kidney function the body may have other means of disposing of an excess of bases; for example, by excretion into the intestine. But if we assume that a considerable portion of the injection is at least temporarily retained, then two possibilities suggest themselves with especial prominence: (1) Acidosis with neutralization of the injected bicarbonate, and (2) retention of the bicarbonate without neutralization. The one factor which speaks most strongly against acidosis is the absence of other signs, such as a high ammonia coefficient. This objection would have still more weight if the excretion of ammonium salts in nephritis were thoroughly understood. Likewise, the subjective disturbances and the febrile reactions which frequently occurred after the injection of bicarbonate may be interpreted as evidence against the idea of an acidosis.

On the other hand, the idea of retention is not altogether simple. It is well known that the diseased kidney retains a variety of substances such as dyes and sugars and certain salts. The mechanism which is involved would appear to be comparatively simple where the substances in question do not react chemically with any constituents of the urine. In the case of bicarbonates which would combine with the acid salts of the urine the problem is more complicated.

Furthermore, inasmuch as one of the normal functions of the kidney consists in the production of acid salts, then on the theory of retention one would be obliged to assume that a lesion of the kidney had brought about an abnormal functional activity as regards the excretion of acids, since the acid salts persist under conditions in which normally a liberal excretion of hydroxyl ions should occur. Indeed if quantities of as much as 50 grams of sodium bicarbonate may be injected into the body and retained without neutralization, then the source of these acid salts in the urine is not readily explained. Furthermore, in one of the cases (No. 8), the kidneys showed extensive diffuse lesions but were able to excrete carbonates readily. However, we are not yet in possession of proof that the kidney in these conditions has become impervious to bases or that it has reached a state comparable to certain cells of the gastric mucosa, for instance, in which only an acid secretion can be produced

Lastly, it should be emphasized that perhaps many factors may be involved in the explanation of a given case and the explanation of different cases may vary widely. Certainly, in many instances, important extra-renal factors may come into consideration. Thus, the nephritis of Asiatic cholera, where the output of ammonia is often very high, may constitute an essentially different condition from the cases reported in the present paper.

Functional Diagnosis and Therapy.—An examination of the data in Table V shows that in all cases in which the tolerance to bicarbonate is markedly increased, the phenolsulphonephthalein output is very low. On the other hand, the excretion of the bicarbonate is practically normal in some of these cases in which the phenolsulphonephthalein test shows a functional insufficiency. It is obvious that there would be many objections to the use of bicarbonate in functional diagnosis. Such a procedure would evidently be less delicate than the phthalein test and it would be complicated by important extra-renal factors.

The study of the majority of substances which are retained by the kidney are of interest from the standpoint of functional diagnosis rather than of therapy. In the case of the bicarbonates, however, the explanation of their behavior might have some bearing on therapy in case it should be shown that they fail to appear in the urine on account of the existence of an acidosis.

The use of the carbonates in the treatment of nephritis has assumed some prominence of late. v. Hösslin [17] reports a reduction in albuminuria following a reduction of the acidity of the urine by the use of sodium bicarbonate. He also noted a marked variation in nephritics in the amount of bicarbonate required to effect a reduction in the acidity of the urine. He administered sodium bicarbonate by mouth in quantities varying from 2 to 15 grams and in one case 24 grams per day. Its use was continued over periods varying from two to four weeks. The acidity of the urine was titrated according to Moritz's method, and from the figures which are given it would appear that, in many instances, the reaction probably became alkaline to litmus. v. Hösslin found many instances in which the albuminuria was not influenced, but recommends that bicarbonate in increasing doses should be tried in all cases of nephritis.

Fischer [18] has recommended the normal carbonate and the results reported indicate a rapid diminution in the albuminuria, a pronounced diuretic action, and a striking improvement in the general condition of the patient.

Perhaps the most hopeful conditions for treatment are those infections in which an acute nephritis may be anticipated and measures may be instituted before its actual development occurs. However, it is certainly desirable to approach the question from something more than an empirical basis.

I am inclined to think that one of the most important factors to determine is whether changes do occur in the kidney which render it incapable of excreting anything but an acid urine even after the introduction of an excess of bicarbonate into the body.

SUMMARY.

The tolerance of the body toward fixed bases has been studied by determining the amount of sodium bicarbonate which must be introduced into the body in order to render the urine alkaline. The following results have been obtained:

In normal individuals the ingestion of five grams of sodium bicarbonate is ordinarily sufficient to bring about the excretion of fixed bases in the urine, its reaction becoming alkaline, though in exceptional cases, this quantity of bicarbonate is insufficient, 10 grams being necessary.

[17] Deutsches Arch. f. klin. Med., Leip., 1912, CV, 147.

[18] Fischer: Loc. cit.

The tolerance to sodium bicarbonate was tested in acidoses produced artificially, in five cases of diabetes, in an obscure toxæmia, accompanied by an increased excretion of ammonia, and in a group of thirteen nephropathies.

A slight grade of acidosis, resulting from a carbohydrate free diet for a period of two to three days produced a small but definite rise in the tolerance to bicarbonate. A similar result was obtained in two cases by the ingestion of small quantities of a mineral acid.

In the five patients with diabetes who were tested, the ordinary signs of acidosis were absent. In three of these patients the tolerance was normal; in two, however, it was definitely increased, the urine remaining acid after the administration of 30 grams of sodium bicarbonate.

In the toxæmic case in which the ammonia excretion was increased there appeared to be a primary disturbance of protein metabolism rather than an acidosis, with a secondary increase in ammonia. The tolerance in this case was normal.

In the study of 13 patients representing several types of nephropathies it was found that four comforming to the general type of a parenchymatous nephritis excreted carbonates, readily behaving in this respect like normal individuals. Consequently the tests on this group do not afford evidence of an acidosis, at least not in the generally accepted sense of the term.

One patient with chronic diffuse nephritis also showed a normal tolerance but none of the remaining patients behaved in a normal manner. Two patients continued to excrete an acid urine after the intravenous injection of sodium bicarbonate in quantities of 60 and 130 grams respectively.

Discussion.

The determination of the tolerance of the body to sodium bicarbonate appears to afford a basis for the development of a method of general application for the detection of acidosis. As far as the clinical interpretation is concerned, it would seem that essentially the same result is obtained by either the intravenous injection or by the ingestion of bicarbonate. Evidence was obtained which indicates that the tissues of the body possess the property of taking up sodium bicarbonate very readily even in the early stages of an acidosis. This may be interpreted as indicating that a slight increase in the acid metabolism is compensated for, in part, by the fixed bases of the body and not wholly by an increase in the excretion of ammonia and of acids.

The interpretation of the ammonia metabolism and the study of the tolerance to sodium bicarbonate are affected in a very different manner by certain conditions which may complicate the detection of an acidosis. Thus an increase in the excretion of ammonia may occur not only in an acidosis but also as the result of a primary disturbance of protein metabolism. In the case of renal lesions, however, the data which are available in the literature indicate that there is no retention of ammonia, and accordingly a nephritis would not interfere with the study of the ammonia excretion. On the other hand, the test for the tolerance to sodium bicarbonate is readily applicable in the presence of disturbances of protein metabolism but the effect of kidney lesions is very obscure. From the limited number of cases reported in this paper it would seem that the one group of nephropathies which do not interfere by reason of the retention of carbonates are those cases which conform to the general type of chronic parenchymatous nephritis. The nephropathies in which the tolerance is increased would interfere with the test if this tolerance is due to retention of bicarbonate on account of the renal lesions.

In the attempt to obtain some evidence concerning the equilibrium between acid and base in the body, many methods have been suggested for the determination of the alkalinity of the blood. However, it would seem that, during pathologic processes when the body is becoming impoverished in certain constitutents, the composition of the blood may be maintained in a relatively normal condition at the expense of the other tissues. For example, when a diminution occurs in the content of the body in carbohydrates or in water, the blood is supplied from the other tissues until their supply is seriously depleted. It seems not unlikely that the same considerations apply in the case of the fixed bases. Consequently, the determination of the tolerance to bicarbonates may afford some information concerning any deficiency which may exist in the content of the tissues in fixed bases; such evidence would be of a very different nature from that obtained by the determination of the reaction of the blood.

In conclusion, I wish to express my appreciation to Prof. L. F. Barker for assistance and for an interest in this work which has been very valuable.

EMBRYONIC BANDS AND MEMBRANES ABOUT THE CÆCUM.

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Some four years ago, under the name of membranous pericolitis, Jackson called attention to what he believed was a distinct form of pericolitis, a definite pathological and clinical entity. This condition is characterized, according to Jackson, by the formation of an entirely new layer of vascularized peritoneum, which is found usually on the ascending colon, often extending up to the hepatic flexure and over on to the transverse colon. In a second report, the original account of the condition has been amplified by the description of an autopsy specimen by Hall, from whose notes the following points are excerpted:

Running from a point near the hepatic flexure to a point three inches above the caput cæci and extending from the parietal peritoneum to the lateral and ventral aspects of the colon, is a thin

vascular veil with long, straight, parallel, unbranching vessels. The appendix is not implicated in any way. With the blood-vessels are long shining bands of connective tissue which gradually broaden and spread out in slight fan-shaped attachments on the anterior and inner surfaces of the colon. The latter is freely movable beneath this membrane. On section, there is no evidence of inflammation, but one finds numerous endothelial lined spaces which suggest a chronic lymph stasis.

While we owe to Jackson the recognition of the possible pathological significance of these membranes, as well as their first accurate description, they have undoubtedly been seen by other observers previous to his report. To Virchow, Hofmeister ascribes the first description, while it is certain that Binnie and Lane had also observed similar structures prior to Jackson's paper.

Since that time cases of so-called membranous pericolitis have been reported by Hofmeister, Connell, Crossen, Pilcher and Gerster, as well as an additional series by Jackson.

The symptoms with which these patients, reported in the literature, suffer may, in general, be classified with those that are already familiar to us in certain types of chronic appendicitis. Pain is ordinarily the thing which makes them seek medical advice. It varies in intensity from feelings of discomfort to a more or less continuous pain on the right side, usually most marked in the right lower quadrant. It is liable to exacerbations and not infrequently accompanied by colic. Tenderness is usually greatest over the cæcum, although palpation may elicit more or less definite response over the entire right side of the abdomen. The patients are usually constipated, especially in advanced cases, although Gerster's series contains several with diarrhœa. The stools may contain mucus, and not infrequently there are gastric symptoms in a sense of fullness after meals with eructations similar to those in appendiceal dyspepsia. Some of the cases have been in undoubted abdominal neurasthenics.

Etiology.

Concerning the etiological factors involved in the formation of these veils, there have been numerous speculations on the part of those who have reported cases. Jackson, to whom we owe our recent interest in them as possible pathological entities, does not venture to ascribe a cause to their formation.

Lane, in discussing the fixation of the cæcum, describes acquired lateral adhesions passing in from the abdominal wall to the cæcum, ascending colon and, in some instances, the proximal portion of the appendix. He states that "The portion of the cæcum above the brim of the pelvis, together with the ascending colon, is retained in a position of abnormal fixity to the posterior wall of the abdomen. This is affected by the development of adhesions between the outer aspect of the large bowel and the peritoneum covering the abdominal wall in its vicinity. In advanced cases, these adhesions are supplemented by a mesentery in which vessels of some size are contained. As a rule these adhesions merely fix the bowel, but occasionally they constrict its lumen very materially in one or more situations and render it liable to become obstructed. Not only do these adhesions anchor this part of the large bowel, but they also bind down to the iliac fossa a portion of the appendix." It is quite certain from this description that the acquired adhesions and mesentery of Lane are identical with the veil described by Jackson.

Binnie considers the membrane to be due to a primary colitis, and that the appendix, if involved, is secondary. Hertzler views them as inflammatory in origin and secondary to affections of the appendix or gall-bladder. These views coincide with those of Hofmeister, who, likewise, looks upon them as structures arising from inflammation in adjacent organs, such as the duodenum, biliary passages, appendix or gall-bladder. Connell, on the other hand, does not regard them as inflammatory in origin, but due to ptosis of the cæcum.

According to Charles Mayo the veils result from "a late rotation of the bowel and descent of the cæcum from its hepatic position after the formation of the parietal portion of the peritoneum in the infant. The cæcum burrows its way into position, as it were, through the peritoneum."

In a recent communication Pilcher expresses himself as follows: "As to the etiology of these films and bands, that view which considers them to be the result of long continued or oft repeated mild infections of the peritoneal coverings of the cæcum and appendix transmitted through the intestinal wall seems to me most probable," while Gerster, the latest contributor on the subject, expresses the view that, "The peritoneum reacts to the infectious processes ordinarily associated with chronic colitis, by the formation of characteristic vascularized transparent membranes (pseudoperitoneum), which take their origin along the external aspects of the cæcum, ascending colon and hepatic flexure."

An analysis of the views expressed by the various contributors to this subject is interesting, for, while there is no question that they are discussing the same structures, yet there is a wide divergence in their opinions as to both the origin and nature of the membranes. Suggestions varying from folds of peritoneum caused by the cæcum burrowing behind the parietal peritoneum in a delayed descent (Mayo), and acquired adhesions to prevent the ptosis of the cæcum (Lane), to various inflammatory or infectious etiological factors (Pilcher, Hofmeister, Binnie, Gerster), have been given as the essential basis of their formation. As it is important for us to know both the origin and the pathological significance of these veils, we have accordingly made it a routine to study carefully the cæcum and ascending colon, with this object in view, whenever we have had access to the right half of the abdomen.

During the past two years I have met with some 29 instances where pericolic membranes of one form or another were found at operation. A detailed account of the histories and findings in these cases would make this paper too voluminous, so simply a summary of the results obtained by a study of these patients will be presented. The pericolic membranes vary widely in their position and distribution, but in almost every instance their physical characteristics are the

same. These fine, filmy structures were well described by Jackson in his first and second papers and to his description of their gross appearance there is little to be added.

So far as their general characteristics are concerned, they are fine, delicate membranes extending over the surface of the first part of the large intestine, which is freely movable under them. They give, as Hall has aptly pointed out, the impression as though the colon were placed in a thin diaphanous bag slightly too small for it. The cobweb veil is very thin and is covered by glistening peritoneum and contains numerous characteristic parallel blood-vessels, which run for a considerable distance without anastomosing. They originate from the vessels of the parietal peritoneum and usually run downwards and forwards to terminate by communicating with the vessels in the muscular coat of the intestine. The attachments of the membranes to both the parietal peritoneum and the intestine are extremely loose and elastic. Here and there, there are firmer strands of connective tissue and the veil terminates usually by spreading out in fan-shaped processes or extensions as it insensibly loses itself in the peritoneal surface of the intestine. The membranes are paper thin and only now and then do they show any deposits of fat. The impression given by them is quite different from that ordinarily conveyed by pathological adhesions. They are neither as opaque nor as avascular as adhesions, and they have, in general, a more or less regular distribution. They are, moreover, much thinner than the parietal peritoneum, as is easily seen when traction is made upon them, for the parietal peritoneum that is pulled out at the points of attachment has the thicker, more opaque appearance that is always seen in hernial sacs.

The histological studies of Hall on this structure, while confined to a single specimen, are accurate and his conclusions that the membranes are not inflammatory seem quite justified.

So far as their distribution is concerned, we have found from our series of cases that they may roughly be divided into three groups. The commonest group is that where the veil extends from the parietal peritoneum along the lateral margin of the colon, particularly near the hepatic flexure, over onto the lateral and ventral aspects of the colon and cæcum. Often the caput of the cæcum is free, but they may extend downwards not only to the caput, but even cover the proximal portion, and sometimes the entire appendix as well.

Another type occurs lower down and extends from relatively the same part of the parietal peritoneum over onto the head of the cæcum and usually covers the proximal half and more rarely the entire appendix. Veils of this description do not, as a rule, extend high up on the ascending colon.

The third type of veil, which is relatively rare, extends from the ventral aspect of the colon and passes over and is continuous with or apparently adherent to the omentum. In some cases, it may extend from the parietal peritoneum on the lateral wall of the abdomen over the ascending colon and then become continuous with the omentum, often holding the ascending and the first part of the transverse colon side by side with a sharp angulation at the hepatic flexure if the latter happens to be long and looped.

Between these three main types of veil there may be intermediate stages or combinations of two types. In fact, each case differs somewhat from the next, but in any considerable number of instances, they will fall more or less naturally into these three groups.

Before we take up the consideration of the nature of these membranes it may be well to consider for a moment the usual peritoneal attachments of the colon and cæcum. In a large percentage of cases, these veil-like structures will be observed about the hepatic flexure, frequently shading off into the omentum, or else making up the supporting reflexion of the peritoneum which extends from the hepatic flexure and over onto the kidney. Likewise, along the lateral and posterior aspect of the ascending colon, tissue, similar in structure to the membranes, will be found holding it (the ascending colon) in place.

Turning, for a moment, to the embryology of this portion of the alimentary tract, the following brief account of the development of the topography and attachments of the first portion of the large intestine, affords the only means by which the origin of these membranes can be explained.

After the reversal or rotation of the gut, the cæcum comes to occupy a position just under the liver about the final site of the hepatic flexure. When the rotation is complete, the mesogastrium balloons forward and the formation of the great omentum begins. This fuses later with the transverse colon and the gastro-colic omentum thus comes into existence. Usually this fusion takes place only along the transverse colon, establishing the usual relationships. Not infrequently, the omental attachments extend further to the right, even to the abdominal parietes. After the cæcum takes up its subhepatic position, there is a fusion between the peritoneal surfaces of the cæcum and the posterior abdominal wall, attaching the large intestine in its new position. As the cæcum descends with the subsequent formation of the ascending colon, the posterior surface of its mesocolon also becomes adherent, thus obliterating the free mesentery of this part of the large intestine. This brief description of the development of the attachments and position of the first segment of the large bowel is of the more frequent types, but here, as elsewhere in the body, we have frequent variations in form, connections, and relationships, as can be seen by studying any large series of cases. Variations in the positions, attachments, time of rotation, and descent are particularly common in this region, as is shown by Smith's study of the relationship of the large bowel in one thousand infants. Now, concerning the nature and position of attachments of the colon to the abdominal wall, we have no careful anatomical studies. Furthermore, embryologists do not possess much detailed information concerning the exact nature of the secondary fusion that takes place between the various layers of the peritoneum, such as the obliteration of the mesentery of the ascending colon and the formation of the attachments of the first part of the large intestine in its final position.

With the usual topography and peritoneal reflections of this part of the large intestine, we are all familiar, as this is what we are accustomed to call the norm. In reality, however,

this is only the predominating type and there are series of less frequent forms which, however, should not be looked upon as pathological, but rather as variations common enough to classify as normal. A study of these less common types, particularly during the stage of their formation and with particular reference to the attachments of the cæcum and adjacent parts of the intestine, may throw some light upon the question of these pericolic membranes.

Through the courtesy of my colleague, Prof. Ferris, I have been able to dissect a series of human embryos and two infants at term and have found conditions which show clearly that these veils are embryonic and normal structures and are not due to the organization of an inflammatory deposit or series of mild infections originating from a chronic colitis.

In the first preparation, an embryo 15½ cm. long, nape-breech measurement, the cæcum (Fig. 5) is still undescended, but the fusion between it and the parietal peritoneum has occurred. Fine veil-like attachments are present, running from the parietal peritoneum just beneath the liver and over the kidney onto the ventral aspect of the cæcum, where they are lost on the mesocæcum. This is an important stage in the development of these pericolic membranes for it represents an excessive degree of fusion of the rotated cæcum with the parietal peritoneum. The usual attachments between the visceral and parietal layers at this point are confined to the posterior aspects of the cæcum and the adjacent portion of the parietal layer. In this case, the appendix lies free in the ileocæcal angle and the terminal ileum is provided with a free mesentery, the posterior leaf of which shows no fusion with the peritoneum.

In an embryo 22 cm. long, nape-breech measurement (Fig. 6), partial descent has occurred. Like the preceding specimen, there are certain atypical and variable features to the attachments between the cæcum and parietal peritoneum. The fusion is most marked at the site of the future hepatic flexure and along the partly formed ascending colon, where the very delicate adhesions marking the fusion of the two layers extend from the parietal peritoneum onto the lateral and ventral surfaces of the colon. The caput cæci is free, but the appendix, caught in these new attchments, shows the effect of the partial descent by being drawn up and kinked along the ventral aspect of the colon with its tip free. It is important to observe that these new-formed attachments which run transverse to the long axis of the colon in the preceding stage, are now drawn partly downwards and are somewhat thinned by the descending cæcum. An effort to lift the terminal ileum reveals that it, too, has partaken in the process of fusion in having the posterior leaf of its mesentery and the posterior aspect of the intestine itself united to the parietal peritoneum by fine, delicate attachments similar to those joining the colon and peritoneum. This is important to bear in mind for, as will be shown later, it represents in its simplest embryonic form a Lane's band.

In an infant at term (Fig. 7), the ordinary conditions found in adult life are present so far as the topography of the cæcum and colon is concerned. Descent has occurred and the omentum is attached to the transverse colon some distance from the hepatic flexure, but a thinned-out portion of the omentum extends over the ventral aspect of the colon as far as the hepatic flexure. Along the lateral margin of the ascending colon, extending from the adjacent portion of the parietal peritoneum and having all of the pericolic veils, are loose membrane-like attachments, the direction of which is now downwards, marking the course of the descended cæcum. The terminal ileum is perfectly free with a mobile mesentery and the appendix is in no way involved in the process of fusion.

Another variation in the usual form of fusion is shown by an embryo 24 cm. long, nape-breech measurement (Fig. 8), where the cæcum is still undescended but is fused posteriorly to the parietal peritoneum over the kidney which can be seen just below the liver and above the cæcum. In this case, no attachments in the form of embryonic membranes extend over the ventral aspect of the colon or cæcum. The appendix, however, is involved in the process of fusion and is attached to the peritoneum just over the kidney, where it shows the effect of the beginning descent in being drawn up and kinked. As is the case in Fig. 6, the tip of the appendix is free, a condition most frequently found in adult life when the appendix is covered by these pericolic membranes.

From a study of these three specimens, it is perfectly clear that unless we accept the unproven theory of fœtal peritonitis, these stages indicate the evolution of the adult pericolic membranes of the commoner type, such as are shown in Figs, 1, 4, 10, and 13, which represent simply a more extensive form of the normal connections between the rotated intestine and the posterior portion of the parietal peritoneum. Usually the fusion takes place only in the approximated portions of the peritoneum and is probably due to some specific chemiotactic action, inasmuch as other parts of the peritoneum at these stages of embryonic life do not participate in the process. At times, however, the fusion is excessive and attachments are formed with the cæcum in the subhepatic position that extend over onto the lateral and ventral aspects of the cæcum and embryonic colon. Given these attachments, the subsequent descent draws them out into the thin veil-like structures that have been described as membranous pericolitis. Both the veils and the parallel vessels in them indicate, as it were, the path of the descent. This process can be appreciated even more readily by reference to the accompanying schema, where the change in position of the cæcum involved in its descent would draw out these fine embryonic adhesions into the form of a veil.

In the series of embryos studied, another infant at term (Fig. 9) throws some light upon the etiology of those veils of the third type which are continuous with the omentum. In this specimen, the following relationships of the cæcum, colon and omentum may be observed: the omentum, with its usual attachment to the transverse colon, extends lateralwards over the cæcum and is attached to the parietal peritoneum adjacent to it. The appendix is free and of the conical infantile type. The fusion between the posterior aspect of the

cæcum and parietal peritoneum has taken place. It must be perfectly obvious that subsequent descent of a cæcum with such omental attachments must give rise (in adult life) to the form of veil shown in Fig. 3, where it extends from the parietal peritoneum over the colon and is continuous with the omentum along its median border. The development of this type of veil may be more readily appreciated from the schema shown in Fig. B, where the superimposed drawings of the earlier and later stages indicate how descent draws out the variable embryonic omental attachments of the cæcum into a pericolic membrane.

These preparations are taken from a relatively small series of embryos, which only serves to emphasize the frequency with which these veils may occur. They naturally vary a great deal in their distribution and extent, but all of those found about the cæcum and ascending colon develop in the manner just described. Surgeons will recognize in these cases where the appendix is involved in the process of fusion, types of appendices which, in adult life, have hitherto been looked upon as resulting from chronic adhesive appendicitis, but which are, in reality, organs that are covered by an embryonic

FIG. A.

FIG. B.

FIG. A.—The black portion of the figure represents the cæcum in its subhepatic position after rotation. The heavy lines the attachments to the parietal peritoneum such as are shown in Fig. 5. It is perfectly clear that subsequent descent would draw out these fine attachments into the form of a veil indicated by the lighter lines.

FIG. B.—The black portion of the figure represents the cæcum in the subhepatic position, with the omentum attached to it and the parietal peritoneum indicated by the heavy black lines. Descent draws out and thins these portions of the omentum into the form of a veil which is continuous with the parietal peritoneum on the one hand and the omentum on the other, as is indicated by the lighter lines.

membrane and not infrequently drawn up and kinked during the descent of the cæcum. In such cases, the cæcum and colon may be free or more frequently involved in the smaller second type of veil. To recapitulate, it will be clearly seen from a study of these specimens, that, after the rotation of the gut, the cæcum becomes attached to the peritoneum of the posterior abdominal wall just under the liver and over the kidney. The precise nature of these secondary attachments has not been worked out by embryologists. In some instances, they are more extensive than in others and may extend out over the surface of the cæcum or ascending colon and, with the subsequent descent, these new-formed connections between the visceral and parietal peritoneum are drawn out in the form of a thin veil, carrying with them their blood-vessels, which take a long unbranching course from their origin on the parietal peritoneum downwards and forwards onto the cæcum or colon, where they communicate with those of the intestinal wall. These secondary unions between the two layers of the peritoneum usually spare the cæcum and extend onto the colon, which give rise to the commoner form of veil (Fig. 1). Occasionally, the cæcum and even the proximal portion of the appendix or, still more rarely, the entire appendix is covered. In such cases, we have the extensive veils which embrace the entire first portion of the large intestine with the appendix drawn up in the process of descent (Fig. 10). In still other instances, the attachments are confined to the region of the cæcum and appendix and thus we have the formation of the veil which simply covers the caput cæci (Fig. 2) with the usual posterior attachments extending up behind the ascending colon.

As there are variations in the form of the secondary attachments between the colon and the peritoneum, so also does the extent of the fusion between the part of the posterior mesogastrium which gives rise to the omentum vary within very considerable limits. Sometimes, the embryonic omentum reaches out lateralwards and fuses with the cæcum before its descent and not uncommonly extends onto the parietal peritoneum. When such a secondary fusion takes place, the cæcum, in its descent drags down the omentum with it and gives rise to that form of veil (Fig. 3) where it is continuous with the omentum along the medial aspect of the large bowel.

Not only from the appearance of the veils themselves, but from the conditions shown in the human embryos and infants just described, it is clear that these pericolic membranes are not the products of inflammation, nor are they the residue of repeated attacks of colitis. It is likewise clear that the view which regards them as the result of a burrowing of the cæcum behind the parietal peritoneum cannot obtain. They represent simply either more marked attachments of the large intestine to the posterior abdominal wall or else, in some cases, a more extensive fusion of the omentum to the colon, which is dragged down with the descent of the cæcum and gives it an attachment on the ascending colon continuous with an embryonic membrane.

SYMPTOMS.

The question of the greatest importance from a clinical standpoint is whether or not these embryonic membranes are ever responsible for symptoms. While, in the great majority of cases, they are not the cause of any trouble to their possessor, I think there is no question, however, that in certain instances, either alone or in combination with other circumstances, they may give rise to symptoms of a very definite nature which are not infrequently either confounded with or associated with chronic appendicitis. When the veils are extensive and badly placed from a mechanical point of view, they may cause obstruction, especially if any degree of ptosis is present. It is not impossible that they may become somewhat thickened as a result of chronic colitis. This is indicated in the denser strands of connective tissue in some veils,

associated with distention of the cæcum, exaggerated or irregular sacculation of the colon, and the unrolling of the intestine after such veils are incised. Veils continuous with the omentum may, if the transverse colon is redundant, hold the hepatic flexure in acute angulation. Patients with such membranes may suffer, not only from the mechanical interference with the intestinal circulation, but may have sensations of pain and distress on the right side more or less exacerbating in character and often show on palpation distinct tenderness over the ascending colon well above the appendix and cæcum. In three instances, my cases have shown points of tenderness over the cæcum or in the pelvis on the right side, as well as a marked reaction high up in the flank. In these cases, the chronically inflamed appendix was found hanging over the brim of the pelvis and a well marked veil on the ascending colon. One instance was in a child of 12, the second in a youth of 18, and the third in a very well nourished woman of 29. In these cases, there was no ptosis; no question of involvement of the kidney and ureter, and no chronic colitis. None of the patients was neurasthenic. There could be no other interpretation of the symptoms and findings at operation, except that the flank pain was due to the constriction of the embryonic membranes. Incision of the veils relieved all three of the cases. That such symptoms may follow their presence is even better shown in the instances reported by Jackson and Connell in which simple appendectomy gave no relief, but where reoperation and removal of the veils accomplished the desired result. A patient upon whom I operated some time ago emphasizes this occasional association of the membranes with symptoms. For years she had suffered with pains of varying intensity on the right side over the cæcum and ascending colon. She was operated upon in the fifth month of a pregnancy complicated by multiple myomata, one of which was strangulated. After the hysterectomy and appendectomy, her condition did not warrant any further interference, so the well marked embryonic veil covering the cæcum and ascending colon was left undisturbed. The appendectomy has had no influence whatever upon the pain on the right side although in other respects she is quite well.

Embryonic veils which embrace the appendix usually kink it and probably are responsible for many of the cases of chronic appendicitis in which they occur. Veils of this type have usually been interpreted as adhesions about the appendix resulting from previous infections. Most operators have frequently been surprised to find a bound-down, kinked and adherent appendix in a case that has never had an acute attack. In such instances the adhesions are usually these embryonic membranes. I have seen two cases where the appendix was constricted and partly obliterated at the point of attachment of a veil, which led to an acute infection of the appendix from the interference of its drainage into the large intestine.

We have come to suspect the presence of these veils as the cause of symptoms in these cases which complain of pain in the right side, usually most marked in the flank and right lower quadrant, which have never had an acute attack of appendicitis and in which the possibility of renal and ureteral involvement can be ruled out. Most frequently, such patients complain of chronic obstruction which usually intensifies their symptoms.

Treatment.

Several suggestions have already been made for the treatment of these pericolic membranes. By some, the veils have been stripped off and the colon denuded of some of its peritoneum in consequence. Another suggestion has been to dissect off the veil and use it as a strand to support the cæcum from sinking into the pelvis. Lately we have simply incised the membrane along the lateral border of the colon and allowed the intestine to unroll and become free. In our first few cases, when we were under the impression that the membrane was inflammatory, we stripped the veil, but later confined any operative interference with it to those cases only where we felt that it was responsible for pain and discomfort or else was offering some mechanical obstruction to the intestinal current. In any case, incision is all that is indicated, for any obstruction can be relieved in this way. Stripping leaves a denuded surface which may lead to the formation of adhesions or cause, in healing, the formation of a new inflammatory membrane which might be worse than the embryonic veil. In those cases where the membrane is continuous with the omentum, the operator may free the omentum by incision and ligation of the bleeding points. By far the best treatment in the majority of cases will be to let them alone, for it must not be forgotten that these are normal embryonic structures of quite common occurrence and they should not be interfered with in the absence of definite indications for their incision or removal. Furthermore, it is especially important to be cautious in attaching any pathological significance to structures which may be simply more or less uncommon anatomical variations of the normal attachments of the colon.

Lane's Band and Kink.

In recent years, everyone has become familiar with the work of Arbuthnot Lane on chronic constipation and the careful study he has made of the mechanical factors that interfere with the fecal current in the intestine. Various aspects of this problem have been discussed by Lane in an interesting series of papers. The great frequency of chronic appendicitis and the association of the disease with chronic obstruction have centered interest more or less upon the band and kink first described by Lane in the terminal portion of the ileum. This condition can best be explained in Lane's own words: "There develops on the under surface of the mesentery of the last few inches of the small intestine a new band, which at first forms part of the under surface of the mesentery. Later it forms a ligament distinct from the mesentery. This ligament contracts and deforms the ileum, producing a kink or obstruction of this portion of the intestine, especially in the erect posture of the trunk. In consequence of this kink, the small intestine becomes very much dilated and this dilatation may extend up as far as the pylorus. The symptoms produced

by this obstruction are superficially very much like those of appendicitis and, in consequence, a large number of normal appendices have been removed to bring about a cure of symptoms resulting from this obstruction, needless to say, without any particular benefit to the patient." Lane, himself, ascribes the formation of the bands to ptosis of the cæcum, a tendency which crystallizes the lines of strain into peritoneal adhesions resulting in a kinking of the gut and a rolling of the intestine on itself. Since the appearance of Lane's papers, a number of observers have reported cases and offered suggestions as to the possible etiology of the condition. Martin, who has studied the problem, reports the results of his investigations as follows: "From a somewhat careful observation of a limited number of cases, I have concluded that the kinking of the ileum within four inches of its cæcum attachment instead of elsewhere, is due to the fact that the ileum at its termination in the large bowel possesses an extremely short mesentery, viz., from one to two inches. Given this comparatively fixed portion of the compressible tube, there are two factors which lead to its distortion: (a) A too movable and displaced large bowel, and (b) an abnormal disposition of the remaining portion of the small bowel or other viscera." Martin does not think that chronic inflammation of either the appendix or adjacent viscera has any particular influence on the formation of these bands. Charles Mayo, also a contributor to this subject, states that: "During the past two years we have observed many cases in which there was a definite kink in the ileum within a few inches of its termination. The ileum was rolled over and fixed upon its mesentery, evidently a condition of inflammatory origin. Sometimes these adhesions, with resulting bands of peritoneum causing a kink, appear to be of congenital development because the condition has been reported in children without evidence of local inflammatory cause. It has been observed that when adhesions were present, or when the peritoneal bands were greatly thickened, the appendix also showed chronic inflammation which was apparently the source of the peritoneal thickening. The relief afforded by freeing the bowel of the adhesions indicates that this is undoubtedly a condition which has much to do with the ill health of the individual, even though the greater number of symptoms were not local but reflex in character, acting upon the stomach and intestines."

In the past two years I have met with 11 cases of Lane's band of which 5 had, at the same time, embryonic veils upon either the cæcum or ascending colon. Of the 11 cases, 8 had marked kinks and the remainder were slight and not associated with any evident obstruction to the lumen of the small intestine. In the gross characters of the bands, none of them looked like acquired adhesions. Some were thin and delicate like the pericolic membranes, while others were thicker and firmer although not of the same character as acquired inflammatory adhesions. On two there were secondary deposits, inflammatory in nature, resulting from attacks of appendicitis. For the most part they extend from the free border of the intestine opposite the mesenteric attachment onto the posterior leaf of the mesentery and thence, if that is short, to the parietal peritoneum over the psoas muscle along the brim of the true pelvis. The discovery of a marked band at autopsy in an infant 11 months old, where neither the illness nor the cause of death was in any way associated with the intestine, forced the conclusion already reached by Mayo that some of these cases were certainly congenital. During the study of the embryos with reference to the attachments of the cæcum and large intestine, a careful inspection of the terminal portion of the ileum was also made to determine just to what extent these bands were present before birth and to see if any rational explanation of their formation could be found.

In this part of the alimentary tract, as in the first portion of the large intestine, there is a great deal of individual variation in both the relations and the attachments of the terminal portion of the ileum. In all of the embryos, except two, the terminal ileum possessed a free mesentery, but it varied considerably in length. In some cases it was short, while in others it was long and free. In almost all cases, however, on the posterior leaf of the mesentery, there was a point of reflection onto the parietal peritoneum over the psoas muscle or just over the brim of the pelvis, the exact point depending on the age of the embryo and the degree of descent that was present. This is well shown in one of the infants at term (Fig. 9), where the mesentery is free and long, but where the cæcum is not yet descended. On lifting the ileum to bring the posterior leaf in view, a distinct fold running from a point near the psoas up onto the posterior leaf is clearly seen. This is the condition which one finds in almost all adults, whether the mesentery is either short or long. In the embryo (Fig. 6) 22 cm. long with a partially descended cæcum, the process of fusion between the cæcum, colon and the parietal peritoneum had apparently involved the terminal part of the ileum as well, so that we have a well marked Lane's band at this stage of fœtal life. As the free part of the ileum is lifted, the delicate attachments that connect the portion adjacent to the ileocæcal valve with the parietal peritoneum are shown. In this instance, union has taken place well down onto the intestine. In a second case, of an embryo (Fig. 8) 24 cm. long, where the cæcum is still undescended, a similar state of affairs is observed except that the posterior leaf is a trifle freer than in the preceding instance. The band was observed for a third time in the case of the 11 months infant noted above (Fig. 12) who died the day after admission to the hospital from cachexia, due to an ovarian teratoma. In this case, the cæcum was undescended, the appendix infantile, and there was a well marked embryonic band uniting the terminal ileum with the posterior peritoneum, almost obliterating the posterior leaf of its mesentery.

In these three instances, occurring in embryonic life and just after birth, we have not only a Lane's band present, but also the explanation of its formation. The band is associated with the fusion that takes place between the rotated intestine and the parietal peritoneum. In all instances, it may not be the result of a direct fusion, for when an attachment takes place in embryos with a short mesentery between the posterior leaf of the mesentery and the parietal peritoneum, while the

ileocæcal junction is still in the subhepatic position, the subsequent descent might tend, owing to the point of fixation, to shorten the posterior leaf of the mesentery and to roll the intestine on itself.

It is probable that this condition is much more frequent than we suspect and that there are many cases where the possession of such a band is not the slightest inconvenience to its possessor. On the other hand there is no question that the presence of these bands may offer serious obstruction to the intestinal current, especially if it is associated with hyperdescent of the cæcum or a condition of acquired ptosis. I think it would be well for surgeons to recall that all cases of pelvic cæcum are not ptotic, for, as Smith has shown in his study of the conditions in 1000 infants, hyperdescent takes place in 10% of the cases and the cæcum lies in the true pelvis. Now, in patients with acquired ptosis or those in whom the hyperdescent is excessive, or those in whom embryonic membranes lie over the cæcum or ascending colon in such a way as to offer obstruction, the presence of these bands may take on a definite pathological significance and become a potent source of delay in the passage of the intestinal contents, not

Fig. C.—Diagram A shows the terminal ileum with its mesentery cut in cross-section. The fine lines represent the embryonic Lane's band. Descent with the cæcum, indicated by the arrow, would tend, owing to the fixation, to roll the intestine on itself and possibly kink it (B).

only in a diminution of the lumen of the gut itself, but in the formation of a definite kink of the ileum as Lane has pointed out.

Symptoms.

The symptomatology in our cases has varied from none attributable to the band itself, but where the disease was chiefly in the appendix, to marked cases with definite obstruction. The differentiation between the symptoms of an obstructing band and chronic appendicitis is often difficult or impossible, as Mayo has pointed out, when the two conditions occur in the same patient.

The symptoms that may be referred to the band are chiefly those of obstruction which is usually chronic. The patients suffer from constipation, the bowels often moving only with the aid of catharsis. There are not infrequently attacks of colic which may be severe enough to simulate an early acute obstruction. In fact, two of my most marked cases had periods of acute obstruction lasting several days. One was operated on for the obstruction. The more usual complaint is one of continual distress or discomfort on the right side low down or about the umbilicus, with frequent severe attacks of pain and colic which are aggravated by the periods of constipation. There are also cases where the referred symptoms predominate and the patient complains chiefly of the distention and eructations of gas. These usually are worse some time after meals. They are, however, not like the characteristic hunger pains of duodenal ulcer. The frequent association of embryonic bands upon the cæcum or colon with kinked or chronically inflamed appendices makes a definite diagnosis of the band alone improbable in very many cases. The usual points of tenderness on the right side along the terminal ileum is not, as a rule, capable of being dissociated from the tenderness of the appendix.

Treatment.

The treatment that has been followed by all surgeons consists in an incision of the band along the mesenteric border of the intestine, allowing the gut to unroll and the kink to straighten out. This can be accomplished with the point of a sharp knife or by passing a pair of anatomical forceps under the band and incising between the blades. It is remarkable how the intestine will unroll and the kink disappear after the release of the constricting action of the band. Martin keeps his patients in the Trendelenburg position after the operation to prevent the reformation of the band by lengthening the posterior leaf of the mesentery and Mayo accomplishes the same result in some patients by smearing the denuded part of the peritoneum with sterile vaseline. We have counted on the usual post-operative distention of the gut to keep the released intestine from either kinking again or allowing obstructive adhesions to form over the area denuded of peritoneum.

Embryonic Bands on the Gall-bladder.

Another type of embryonic band which is familiar to anatomists and embryologists, but to which no one, so far as I am aware, has ascribed a definite symptomatology, is a small band like a mesentery which extends from the gall-bladder onto the transverse colon to become continuous with the omentum. It is thin, relatively avascular, and contains but little fat. In some cases the fundus is free and in others the mesentery extends well up to the tip of the organ. Attention has again been called to this omental mesentery of the gall-bladder recently by Rubin in his interesting paper on the functions of the omentum. He states that he has only observed the condition in children and infants where pathological changes are out of the question. Recently, I found in the same infant (who had died of an intercurrent disease) an example of this variation of the omental attachment, with a Lane's band and undescended cæcum. It was apparent that this was simply an embryological band such as has been frequently seen and owed its origin to the fundus catching up a portion of the omentum as it grew out from the common duct. A few weeks later, a patient entered the hospital with the following rather remarkable history:

The patient, Miss D., is an extremely intelligent young woman of 20. About three years ago she fell and received a blow on the abdomen just above the hip. Since that time she has had a constant pain on the right side which becomes very sharp and radiates to the right shoulder on any extra exertion, especially like jarring or twisting the right side. Indigestion or accumulation of gas in the intestines increases the pain in the side. On taking a deep breath a sharp pain is noticed in the right hypochondrium (patient points to the gall-bladder region). Recently she has much discomfort in the epigastrium, especially after eating, when she feels as though her stomach is distended with gas. Her bowels are more constipated, a condition which dates practically from the onset of the present illness. She has no nausea or vomiting, the attacks are not associated with fever or feelings of general malaise. The general physical examination is negative. There is no tenderness or fixation of the spine; sacro-iliac and hip joints negative. The abdomen is soft and everywhere tympanitic. Stomach tympany not increased. There is distinct tenderness on deep palpation over the gall-bladder. Along the right flank there is also a slight response to deep palpation. Over the region of the cæcum at Lantz's point there is an area of tenderness with a sharp muscle spasm on deep palpation. Rectal examination negative. The urine is clear and the kidneys are neither felt nor tender.

At the operation, a well-marked embryonic veil was found extending down from the parietal peritoneum near the hepatic flexure over onto the ascending colon and cæcum. The membrane embraced the proximal part of the appendix. The appendix was removed and the veil incised. An exploration of the gall-bladder showed an embryonic band like a mesentery extending from the cystic duct up to the fundus over onto the transverse colon, where it was continuous with the omentum. Its character was exactly like that of the one found in the infant. This band was incised so that the gall-bladder and colon were liberated. There was no question of any inflammatory reaction about the gall-bladder. It had a smooth and glistening peritoneum, was not thickened, and its contents could be squeezed by gentle pressure into the duodenum. It contained no stones.

This case presents many interesting features. The patient had carried the pericolic membrane and the mesentery of the gall-bladder from birth without symptoms until the time of her fall, when the supports of the large intestine were probably weakened so that the band about the colon began to interfere with its function and a certain amount of traction was exerted on the gall-bladder by its omental mesentery when the patient took a deep breath or indulged in extra or unusual exertion. On such occasions the characteristic pain of the gall-bladder radiating to the shoulder would occur. Liberation of both bands relieved her of the symptoms completely. The patient had three points of tenderness, namely, the gall-bladder, the ascending colon and the appendix. Bands on the two former organs were responsible for pain and tenderness, while the chronic inflammation of the appendix was brought about by the extension of the veil over its proximal portion.

The conditions presented by these patients with embryological bands all simulate to a greater or less extent conditions that are familiar to us in chronic appendicitis. A differentiation between them is often difficult, and sometimes impossible, when the two conditions occur simultaneously in the same patient. The point to be learned is that a group diagnosis of chronic appendicitis will leave many unbenefited patients if the therapy is limited to an appendectomy. The day of inch incisions for appendicitis is over and every case of chronic appendicitis should have an incision large enough to afford an opportunity to explore the terminal ileum and ascending colon. Such an incision heals as strongly as a small one if it is properly closed. A patient who takes an anæsthetic is entitled to have a visual exploration of the accessible portion of the abdomen made to supplement the less accurate clinical and pre-operative methods of diagnosis and investigation.

The study also emphasizes that we should ascribe pathological significance to normal, but variable, structures with great hesitation. It is also essential to be familiar with the type variations of the different viscera. Difficulties in the interpretation of pathological conditions thus become simpler and the attempt to restore normal relationships easier.

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EXPLANATION OF PLATES.

FIG. 1.—Common type of membrane extending from the parietal peritoneum near the hepatic flexure downwards over onto the ventral aspect of the ascending colon. Caput cæci and appendix free.

FIG. 2.—Embryonic membrane extending from the parietal peritoneum over onto the caput cæci, involving the proximal portion of the appendix, which is kinked.

FIG. 3.—Embryonic membrane extending from the parietal peritoneum near the hepatic flexure onto the ascending colon and cæcum. With the exception of the tip, the entire appendix is covered by the veil. The membrane extends across the colon and is continuous with the omentum.

FIG. 4.—Marked veil over the colon, cæcum, and proximal portion of the appendix, which is kinked and drawn upwards during descent. Note the thickened strands of connective tissue in the membrane causing irregular sacculation of the cæcum and colon. A well-marked Lane's band is present.

FIG. 5.—Human embryo 15½ cm. long. Cæcum undescended. Secondary fusion between the parietal peritoneum and cæcum. These secondary attachments between the parietal peritoneum and the embryonic intestine extend over the cæcum and colon to the mesocæcum and mesocolon. Descent of the cæcum in a case like this leads to the formation of an embryonic membrane such as is shown in Fig. 1. The caput cæci, appendix, and terminal ileum are free.

FIG. 6.—Human embryo 22 cm. long. Cæcum partly descended. Embryonic membrane extending over the appendix and ascending colon. Elevation of the terminal ileum reveals the fusion between the posterior leaf of the mesentery and the ileum itself in the form of an embryonic Lane's band. With an attachment like this, the ileum may roll on itself during descent.

FIG. 7.—Infant at term. Cæcum descended. Well-marked embryonic membrane extending from the parietal peritoneum over the ascending colon and cæcum. Such a membrane results from

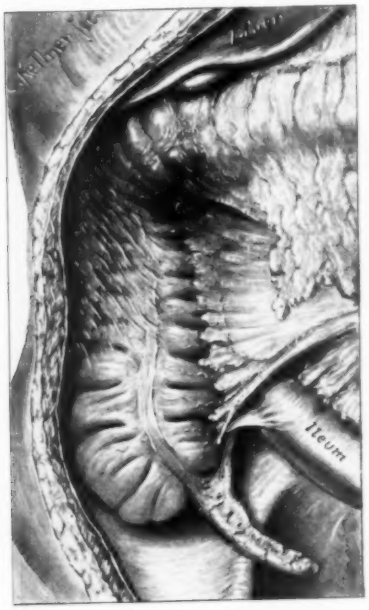

FIG. 1.

FIG. 3.

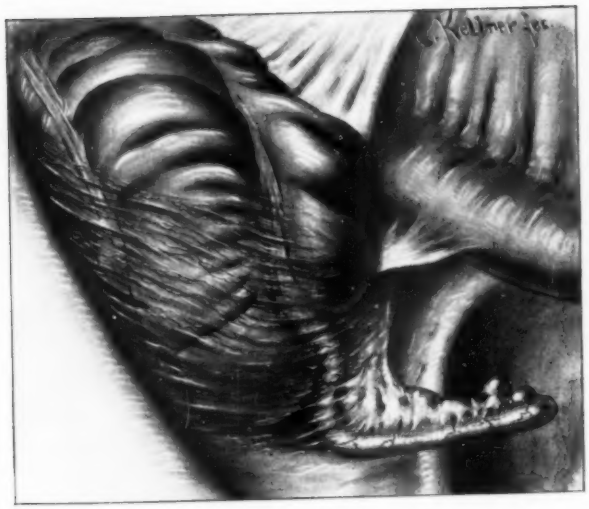

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FIG. 4.

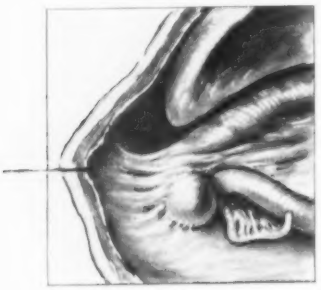

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FIG. 6.

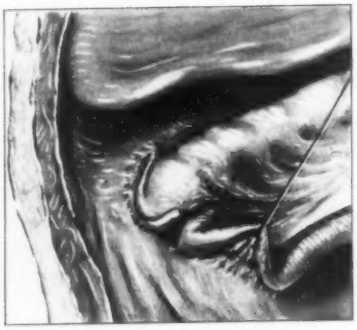


FIG. 8.

FIG. 7.

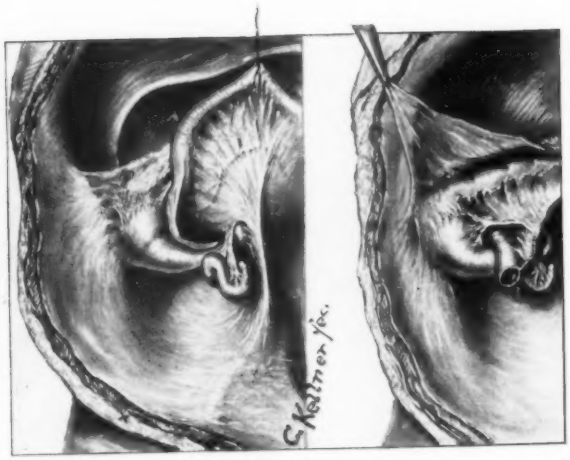
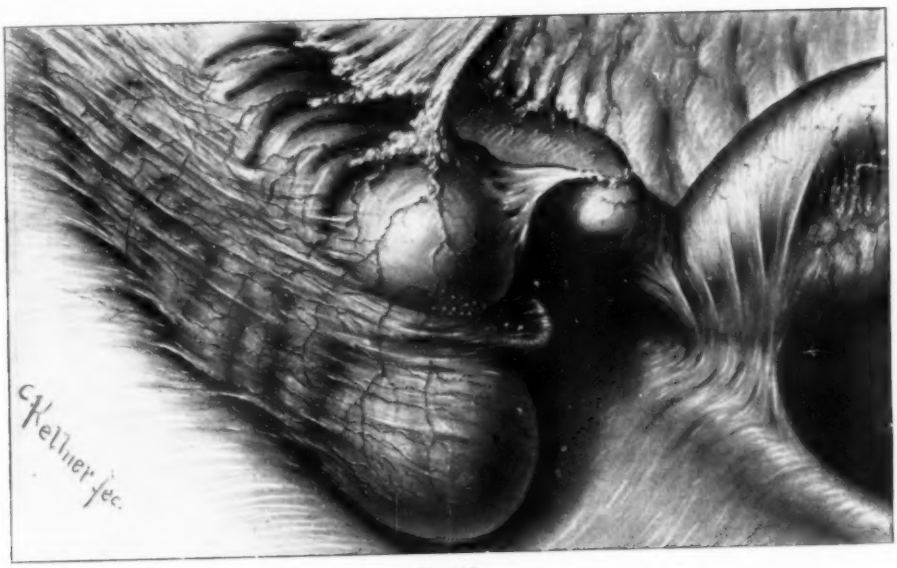


FIG. 9.



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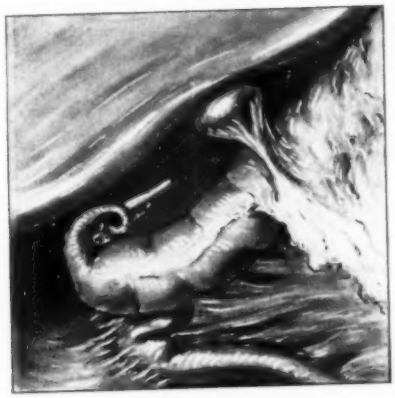

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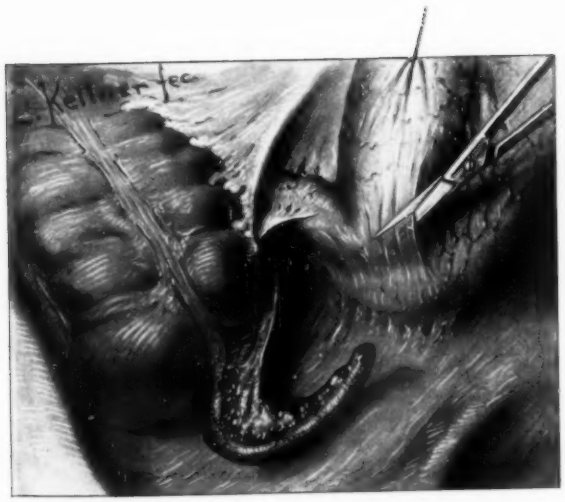

FIG. 11.

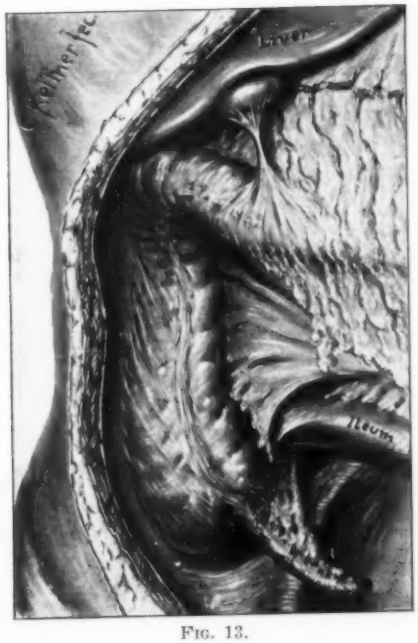

FIG. 13.

the descent of the cæcum when the attachments in earlier embryonic life are like those shown in Fig. 5. This represents the embryonic form of the membrane illustrated in Fig. 1. The appendix and terminal ileum are free.

Fig. 8.—Human embryo 24 cm. long. Cæcum undescended. Cæcum fused to the parietal peritoneum, the process involving the appendix, which is kinked. The terminal ileum shows a partial fusion to the parietal peritoneum forming an embryonic Lane's band. It is this type of fusion when it extends onto the caput cæci that gives rise to the type of veil shown in Fig. 2.

Fig. 9.—Infant at term. Cæcum undescended. Extensive attachment of the omentum over the cæcum and ascending colon to the parietal peritoneum. Subsequent descent of the cæcum with omental attachments of this nature gives rise to the form of veil shown in Fig. 3. Elevation of the ileum shows the reflexion of the parietal peritoneum onto the posterior leaf of the mesentery. This is the common type seen in adult life.

Fig. 10.—Marked Lane's band showing the kink and rolling of the intestine resulting from embryonic fusions between the terminal ileum and parietal peritoneum such as are shown in Figs. 7 and 8. There is also a well-marked embryonic membrane extending over the ascending colon and cæcum involving the appendix, which is drawn up behind the cæcum during descent.

Fig. 11.—Marked Lane's band and kink causing obstruction and dilatation of the small intestine.

Fig. 12.—Infant 11 months old. Cæcum undescended. Lane's band. Omental mesentery to the gall-bladder.

Fig. 13.—Omental mesentery to the gall-bladder causing symptoms. Embryonic membrane over colon, cæcum, and proximal portion of the appendix.

REFLEX ALBUMINURIA.

RENAL ALBUMINURIA SECONDARY TO IRRITATION OF THE URINARY BLADDER.

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Studies in metabolism conducted upon dogs, in which the urine may be obtained by means of a catheter or, perhaps, through a cannula sewn into the bladder, are often complicated by the appearance of more or less albumin in the urine. At first thought, one might assume that this albumin was derived from the irritated bladder mucosa, but the amount is considerable at times, and we shall attempt to show that this albumin in great part is derived from the kidneys. It seems that this is a true renal albuminuria and that some nervous reflex must be responsible for it—that transient or continuous irritation or inflammation of the bladder mucosa can cause a true reflex response on the part of the kidney. The path of this reflex will be interesting to investigate, as well as the action of various other stimuli upon the bladder or organs in the immediate neighborhood supplied by the same plexus.

In some cases this reflex is so prompt and noticeable as to remove all doubt in one's mind concerning the possibility of ascending infection along the ureters. Whether the arc is completed by the sympathetic chain or not is still to be determined, but it is an interesting observation that the renal epithelium can respond so actively to certain localized outside stimuli.

It will be rather easy to approach this problem in the case of human beings, especially in females. It is not difficult to imagine some long-standing source of irritation (calculi, tumors or cystitis) which might be associated with an albuminuria of slight or progressive degree. A constant albuminuria will be associated with casts and a certain grade of stagnation of urine in the tubules, which will handicap the kidneys and lead to further injury—a vicious circle with progressive degenerative changes. If this handicap is imposed on kidneys already diseased, it may cause a progressive injury to the renal epithelium and bring about sufficient damage to overwhelm kidneys which may be working close to their maximum capacity.

That the presence of calculi in the ureter or kidney pelvis may cause interesting reflexes is familiar to all, but we have not found any observations upon the point in question—the reflex action of bladder irritation upon the kidney secretion.

Paschkis reports some cases of vesical calculi showing albumin in the urine, and Eastmond reports two cases having renal symptoms with bladder calculi but neglects to say of what nature these symptoms were. Fenwick gives an account of an inflammation at the umbilicus resulting in a reflex cystitis, and calls attention to the difference between the embryological relationship that exists between the umbilical region and the bladder and that between the kidney and bladder. Upon the knowledge of this difference he expresses the opinion that, having an ascending infection and possibilities of obstruction, a bladder calculus has no influence on the functioning of the tract. As opposed to this, Lewis expresses the opinion, based upon observation of his own cases, that a calculus anywhere in the urinary tract will cause albuminuria but makes no further observation bearing on the question under consideration here. Treves reports in brief the case of a Newfoundland dog which died of uræmia and showed at autopsy normal kidneys and a large bladder stone.

Method 1.

Dogs were used in all these experiments and usually fox terrier females, as they were best suited for our purpose. Only in very young dogs was it needful to dilate the vagina, and in no instance was the vagina cut to expose the urethral papilla, which favors bladder infection. Before operation the urine was invariably tested for albumin, and, as a rule, the dogs were rejected which showed existing albuminuria. In our experience an albuminuria of ¼ gm. per litre (Esbach) is not a very infrequent finding in healthy dogs—especially older animals. The animals

were kept the greater part of the time in large cages but were allowed to exercise in the yard at various times.

The foreign bodies introduced into the bladder were various. The common five-cent piece, weight 5 gm., diameter 2 cm.: marbles, which were soaked in acid to remove their smooth coating and filed to further roughen the surface, weight 3.2 gm., diameter 1½ cm.; buttons, the common metal collar button and the familiar enameled bachelor's button with two separate parts which snap together, weight 2.5 gm., diameter 1.7 cm.

All operations were done under surgical ether anæsthesia with aseptic precautions. Only the more complete experiments are cited here, but all our observations were in harmony and we believe that the experiments detailed below are sufficient to make our points clear. Urine was usually obtained by catheter, but when this was not available it was collected under a clean metabolism cage. Dogs with a certain grade of cystitis are apt to urinate very frequently, and it is often difficult to obtain any considerable amount by catheter.

Albumin was detected in the urine by familiar clinical methods. (1) Heller's nitric acid contact test, with urine diluted with equal volumes of distilled water. (2) Heat and dilute acetic acid. (3) Esbach's test, using the reagent modified by Tsuchiya (phosphotungstic acid 1½ gm., concentrated hydrochloric acid 5 cc., and ethyl alcohol to a volume of 100 cc.). In this test the urine was first diluted with equal volumes of distilled water.

In washing out the bladder to obtain urine free from exudate from the bladder mucosa, it was found best to give the dog a large amount of water by stomach tube and await the appearance of a brisk diuresis. When the diuresis was at its height the animal was placed upon a table, a catheter inserted and the bladder washed out repeatedly until the washings gave not the slightest evidence of any albumin. Urine was collected during the next few minutes, and this was looked upon as practically pure renal secretion, for it is difficult to believe that the degree of cystitis usually present could add any appreciable amount of albuminous exudate to the urine during this short time.

The catheterization of the ureter was done usually on the left side, with as little handling of the tissues as possible. A small glass cannula was tied into the cut ureter a few centimeters below the pelvis, the urine collected, and later the kidney was extirpated. Under anæsthesia it is necessary to give normal saline solution intravenously to promote a satisfactory diuresis.

Gross and histological examination of the kidney removed at operation or the entire urinary tract at autopsy was made in every instance. The ureters and pelves were examined with especial care. The tissues were fixed usually in formalin and stained in the routine manner.

Dog B-24.

1-9-'12. Dog, female, fox terrier, weighs 10.7 kilos (23.5 lbs.), in good condition.

Operation: A five-cent piece was introduced into the urinary bladder.

1-13-'12. 71 cc. of urine pipetted from floor after giving animal 300 cc. of water by the stomach tube.

1-16-'12. Animal weighs 10.3 kilos (22¾ lbs.) and is in good condition.

1-25-'12. Animal weighs 9.5 kilos (21 lbs.) and is in good condition.

1-27-'12. Gave 300 cc. of water by stomach tube. Diuretic time about 1 hour and 15 minutes (height of diuresis attained in 1¼ hrs. after giving the water).

1-30-'12. Gave 300 cc. of water by stomach tube. Diuretic time about 1 hour and 30 minutes.

2-1-'12. Animal weighs 9.4 kilos (21¾ lbs.) and is in good condition. Gave 400 cc. of water by stomach tube. Bladder was washed as described above. Could not get urine for test.

2-3-'12. Gave 500 cc. of water by stomach tube. Washed out bladder in usual manner. Collected urine during first 10 minutes of the washing (see table) and again at end of first 20 minutes after washing (see table). Albumin and few casts present.

2-6-'12. Gave 500 cc. of water by stomach tube. Washed out bladder in usual manner and collected urine for the following 15 minutes.

2-8-'12. Animal weighs 9.5 kilos and is in good condition.

2-10-'12. Gave 500 cc. of water by stomach tube. Washed bladder in usual manner and collected urine during the first 15 minutes following washing (see table).

2-13-'12. Gave 500 cc. water by stomach tube at 11 a. m., 700 cc. at 1.15 p. m. and 300 cc. at 2.30 p. m.

Operation: Catheterized left ureter about 3 cm. from pelvis of kidney.

3.45 p. m. 40 cc. of urine from bladder by catheter.

3.50 p. m. Began infusion of sterile salt solution into right femoral vein.

4.10 p. m. 500 cc. salt solution infused.

4.20 p. m. 400 cc. salt solution infused. Urine started and flowed and bladder was catheterized (see table).

5.35 p. m. 1600 cc. salt solution infused (total). Bladder catheterized (see table), and kidney removed.

2-14-'12. Animal died at 5.30 p. m.

Autopsy. 5.40 p. m. Kidneys: Acute congestion, otherwise normal. Ureters: Normal. Bladder: Subacute cystitis. Lungs: Bronchopneumonia and œdema. Other organs normal.

Microscopical sections: Kidney removed at operation. The cortex shows congestion of all the vessels. The stroma everywhere is normal. The epithelium of the convoluted tubules is perfectly normal, and the glomeruli also are normal. The vessels of the pyramids are greatly congested. The epithelium of the collecting tubules shows a moderate grade of fat in fine droplets. Kidney removed at autopsy presents an identical appearance with the other. Bladder: The epithelium is intact. It is considerably thickened, and the papillæ in places are very conspicuous. There is a suggestion of metaplasia of the epithelium in places. The submucosa shows engorged thickened vessels. It is definitely thickened and the tissue is infiltrated with large numbers of mononuclear cells, with occasional polymorphonuclear cells.

Summary, Dog B-24.—A strong female fox terrier was operated upon and a five-cent piece introduced into the urinary bladder. The urine before operation was negative for albumin and casts. For a few days following the operation a large amount of albumin was present in the urine. Albumin was constantly present during the three weeks following the operation after the animal was active and in perfect health, the wound healing per primam. *Casts* were first noted at the end of the third week and were constantly present in small numbers after this. After a space of four weeks the dog was given 500 cc. of water by stomach, and after diuresis was active, the bladder was rinsed out thoroughly and the urine collected during the next 10 minutes. This dilute urine contained considerable *albumin*, and it seemed certain that this albumin must have been derived from the renal and not from the bladder epithelium. A few casts were present. The same procedure a few days later gave identical results. Albumin was present in the dilute urine—¾ gm. to the litre.

At the end of five weeks the dog was operated upon and the left ureter catheterized. Diuresis was stimulated by intravenous injection of normal saline solution. Urine collected from the ureter and washed bladder showed *albumin*

constantly present in about equal amounts. The dog had aspirated some vomitus into the bronchi during the ether anæsthesia and died the next day with extensive pneumonia of one side. The autopsy was made at once and showed normal kidneys, both the one removed at operation and that removed at autopsy. The ureters and pelves were normal. The bladder showed a moderate grade of subacute cystitis, especially about the opening of the urethra.

2-3-'12. Gave 500 cc. of water by stomach tube. Washed bladder 6 times, with 50 cc. of water each time, until the last washing showed negative albumin test. 3 cc. of urine collected during 5 minutes after last washing.

2-6-'12. Gave 500 cc. of water by stomach tube. Washed bladder as before.

2-8-'12. Weight 9.4 kilos (20¾ lbs.). Animal in good condition.

2-10-'12. Gave 500 cc. of water by stomach tube. Washed bladder as before. Urine collected for 15 minutes following washing.

DOG B-24.

Date. 1912.	Amt. of urine in cc.		Reaction of urine.	Albumin.				Casts.	Cells.			Remarks.
	Cage.	Catheter.		Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.	
Jan. 9..	....	114	Acid.	Neg.	Neg.	....	.....	Neg.	Neg.	Neg.	Neg.	.....
	Operation: Foreign body introduced into bladder.											
Jan. 12..	60	..	Ac.	Heavy.	Heavy.	....	.....	0	+	+	Few.	.....
Jan. 13..	95	..	Ac.	Heavy.	Heavy.	....	.....	0	+	+	Few.	.....
Jan. 13..	...	71	Ac.	Moderate.	Moderate.	....	.....	0	+	+	Few.	.....
Jan. 14..	130	..	Ac.	Moderate.	Moderate.	....	.....	0	+	+	Few.	.....
Jan. 14..	...	50	Ac.	Moderate.	Moderate.	....	.....	0	+	+	Few.	.....
Jan. 15..	60	..	Ac.	Moderate.	Moderate.	....	.....	0	Few.	Few.	Few.	.....
Jan. 16..	65	..	Ac.	Light.	Light.	....	.....	0	Few.	Few.	Few.	.....
Jan. 16..	80	..	Ac.	Light.	Light.	....	.....	0	Few.	Few.	Few.	.....
Jan. 18..	...	35	Ac.	Light.	Light.	....	.....	0	Few.	Few.	Few.	.....
Jan. 21..	250	..	Ac.	Lignt.	Moderate.	....	.....	0	Very few.	Very few.	Few.	.....
Jan. 21..	28	..	Ac.	Moderate.	Moderate.	....	.....	0	Very few.	+	Few.	.....
Jan. 22..	50	..	Ac.	Moderate.	Moderate.	½	.....	0	Few.	+	Few.	.....
Jan. 23..	35	..	Ac.	—	Moderate.	....	.....	0	—	—	—	.....
Jan. 24..	105	..	Ac.	Moderate.	Heavy.	1¾	Dirty gray.	0	+ +	+	+	.....
Jan. 25..	...	18	Ac.	—	Heavy.	....	.....	—	—	—	—	.....
Jan. 25..	...	15	Ac.	Moderate.	—	½	.....	.....	+ +	+	Few.	.....
Jan. 26..	250	..	Ac.	Faint.	Distinct.	⅓	.....	A few hyal. and gran.	+	+	Very few	.....
Jan. 27..	60	..	Ac.	Heavy.	Heavy cloud.	2	Dirty green.	—	—	—	—	.....
Jan. 27..	...	15	Neut.	—	—	....	.....	A few gran.	+	Few.	Few.	.....
Jan. 28..	250	..	Ac.	Faint.	Moderate.	½	Light gray.	A few hyal. and gran.	+	Few.	Few.	.....
Jan. 29..	85	..	Ac.	Moderate.	Moderate.	1½	.....	Very few hyal.	+ +	+	Few.	.....
Jan. 30..	...	32	Ac.	Moderate.	Moderate.	½	Green.	Very few gran.	+	Very few.	Few.	.....
Jan. 31..	410	..	Ac.	Moderate.	Moderate.	⅓	.....	Hyal. and gran.	Very few.	Few.	Few.	.....
Feb. 1..	...	15	Ac.	Moderate.	—	....	.....	Very few hyal.	+	Very few.	+	.....
Feb. 2..	280	..	Ac.	Moderate.	Moderate.	¾	.....	Neg.	Neg.	Neg.	Few.	.....
Feb. 3..	...	28	Ac.	Heavy.	Moderate.	⅓	White.	A few gran.	Neg.	+	+	.....
(a)..	...	6	Ac.	—	Moderate.	....	.....	—	—	—	—	Bladder washed and urine collected during diuresis.
(b)..	...	6	Ac.	—	—	....	.....	A few gran.	Neg.	+	+	
Feb. 4..	500	..	Neut.	Heavy.	Heavy.	1	.....	A few gran.	Neg.	Neg.	Few.	.....
Feb. 5..	50	..	Ac.	Heavy.	Heavy.	3	.....	Gran. and hyal.	Few.	Few.	+	.....
Feb. 6..	185	..	Ac.	Heavy.	Heavy.	1	Dark gray.	Very few hyal.	Neg.	Neg.	+ +	.....
Feb. 8..	...	25	Ac.	—	Heavy.	¾	Pale gray.	Many hyal. and gran.	Neg.	Neg.	+ +	Bladder washed and urine collected.
Feb. 7..	550	..	Ac.	Heavy.	Heavy.	⅓	.....	Very few hyal. and gran.	+	+	+	.....
Feb. 8..	...	30	Ac.	Heavy.	Heavy.	2	.....	Some gran.	+	+	+	.....
Feb. 9..	100	..	Ac.	Moderate.	Heavy.	1½	.....	A few gran.	+ +	+ +	+	.....
Feb. 10..	±	..	Ac.	Moderate.	Heavy.	½	.....	Neg.	+ +	+ +	+	.....
Feb. 10..	...	±?	....	—	Definite.	....	.....	—	—	—	—	Bladder washed and urine collected.
Feb. 12..	200	..	Ac.	Light.	Light.	¾	.....	A few gran.	Neg.	Few.	Neg.	.....
Feb. 13..	50	3	Ac.	—	Light.	....	.....	.....	+	+	Few.	.....
Feb. 13	Operation: Ureter catheterized.											
4.30 p. m.	....	8.0	.....	.....	.....	....	.....	.....	.....	.....	.....	Urine from ureter.
4.40 p. m.	....	2.5	.....	.....	Heavy.	....	.....	—	—	—	—	
5.00 p. m.	....	6.0	.....	.....	.....	4	White.	—	—	—	—	
5.20 p. m.	....	9.0	.....	.....	.....	2	White.	A few hyal. and many gran.	Neg.	+	+	
5.35 p. m.	....	2.8	.....	.....	Moderate.	....	.....	.....	—	—	—	Urine from bladder.
(a)..	....	40	.....	.....	Heavy.	1+	White.	.....	.....	.....	.....	Urine from bladder after operation.
(b)..	....	17	.....	.....	Moderate.	1+	White.	A few hyal. and gran.	+ +	+	+ +	

Dog C-16.

1-16-'12. Dog, female, fox terrier, mongrel, weight 8.4 kilos (18½ lbs.), in good condition. Urine negative.

1-20-'12. Operation: A marble was introduced into the bladder. Weight of animal 9.1 kilos (20 lbs.), in good condition.

1-21-'12. Animal in good condition. Wound dry.

1-22-'12. Animal lively.

1-25-'12. Weight 8.9 kilos (19.5 lbs.). Animal in good condition.

1-30-'12. Gave 350 cc. of water by stomach tube. Diuretic time 50 minutes. Motile bacteria in specimen of urine.

2-1-'12. Gave 350 cc. of water by stomach tube. Diuretic time 1 hour. Weight 9.1 kilos (20 lbs.).

2-15-'12. Weight 8.6 kilos (19 lbs.). Animal in good condition.

2-21-'12. Animal not very lively.

2-22-'12. Weight 8.9 kilos (19.5 lbs.). Animal in good condition.

3-30-'12. Weight 9.1 kilos (20¼ lbs.). Animal very fat and in good condition.

Operation: Catheterized left ureter.

11.48 a. m. Began salt infusion into right femoral vein.

12.05 p. m. 500 cc. salt infused.

12.09 p. m. Urine started to flow.

12.31 p. m. 1000 cc. salt infused (see table).

1.02 p. m. 1500 cc. salt infused.

1.12 p. m. 1600 cc. salt solution infused (total).

1.15 p. m. (see (a), table). Catheterized bladder urine.

1.35 p. m. Kidney removed, weight 34.5 gm. Normal throughout.

4-1-'12. Animal died during night.

Autopsy, 1.30 p. m. Right kidney weighed 32 gm. Cortex measured 7 mm. Normal. Ureters normal except for some dilatation of the lower 3 cm. of their length. Bladder: Subacute cystitis. Lungs: Beginning bronchopneumonia and œdema. Abdomen: Acute peritonitis, surgical sponge left in abdominal cavity. Other organs negative.

Microscopical sections: Kidney removed at operation shows perfectly normal stroma, tubules and glomeruli. Kidney removed at autopsy shows perfectly normal stroma and glomeruli. The epithelium of the convoluted tubules shows post-mortem change. There is a small fibroma in the pyramid. The bladder shows an intact epithelial covering which is somewhat thickened. The submucosa is greatly thickened and is full of dilated vessels. Wandering cells are very numerous here, chiefly mononuclears. The other organs are negative.

Summary, Dog C-16.—This experiment was practically identical with preceding one (Dog B-24). The urine was negative before operation and insertion of a marble into the bladder. Albumin was constantly present after this time. Casts appeared after a period of ten days. Urine obtained at different intervals (weeks or months after operation) from the washed bladder or from the catheterized ureter during diuresis, showed constantly albumin in considerable amounts ($\frac{1}{2}$ to 2 gm. to the litre). It seems certain, then, that the greater part of the albumin found in the daily urine was excreted by the activity of the renal epithelium and not by the bladder mucosa.

DOG C-16.

Date.	Amt. of urine in cc.		Reaction of urine.	Albumin.				Casts.	Cells.			Remarks.
1912	Cage.	Catheter.		Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.	
Jan. 18..	....	45	Ac.	Neg.	Neg.	—	.....	Neg.	Neg.	Neg.	Neg.	.....
Jan. 20..	....	60	Ac.	Neg.	Neg.	$\frac{1}{10}$	Dirty green.	Neg.	Neg.	Neg.	Neg.	.....
Jan. 20	Operation: Marble placed in bladder.											
Jan. 22..	100	....	Ac.	Heavy.	Heavy.	....	.....	Neg.	+ +	Neg.	Neg.	.....
Jan. 23..	100	....	Ac.	—	Heavy.	....	.....	Neg.	+ +	Neg.	Neg.	.....
Jan. 24..	125	....	Ac.	Very heavy.	Very heavy.	$5\frac{1}{4}$	Pink.	Neg.	+ +	Few.	Veryfew	.....
Jan. 25..	90	....	Ac.	Very heavy.	Very heavy.	$6\frac{1}{2}$	.....	Neg.	+ +	Few.	Veryfew	.....
Jan. 26..	220	....	Ac.	Heavy.	Heavy.	3	.....	Neg.	+ +	Very few.	Veryfew	.....
Jan. 27..	110	....	Ac.	Heavy.	Heavy.	$4\frac{1}{2}$	.....	Neg.	+	Few.	Few.	.....
Jan. 28..	250	....	Ac.	Heavy.	Heavy.	3	Pink.	Neg.	+	+	Few.	.....
Jan. 29..	180	....	Ac.	Moderate.	Heavy.	3	.....	Neg.	+	+	+	.....
Jan. 30..	250	....	Ac.	Moderate.	Heavy.	$\frac{1}{10}$	Light gray.	Neg.	Few.	Neg.	Few.	.....
Jan. 30..	150	....	Ac.	Light.	Light.	....	.....	Few gran.	Neg.	Neg.	Few.	.....
Jan. 31..	345	....	Ac.	Moderate.	Moderate.	$\frac{1}{2}$	.....	Few hyal.	+	Very few.	Neg.	.....
Feb. 1..	180	....	Ac.	Moderate.	Moderate.	$\frac{1}{4}$	.....	—	—	—	—	.....
Feb. 2..	200	....	Ac.	Moderate.	Moderate.	$\frac{1}{4}$	.....	A very few hyal.	Few.	Few.	Few.	.....
Feb. 3..	120	....	Ac.	Moderate.	Heavy.	$\frac{1}{2}$	White.	Numerous hyal. and gran.	Neg.	Neg.	+	.....
Feb. 3..	....	3	Ac.	—	Heavy.	....	.....	—	—	—	—	Bladder washed and urine collected during diuresis.
Feb. 4..	300	....	Ac.	Moderate.	Moderate.	$\frac{1}{2}$	.....	Hyal. and gran.	+	+	+ +	.....
Feb. 5..	150	....	Ac.	Heavy.	Heavy.	$3\frac{1}{2}$	.....	Gran.	+ +	+	+	.....
Feb. 6..	135	....	Ac.	Moderate.	Moderate.	$\frac{3}{4}$	Dirty gray.	Hyal. and gran.	+	+	Few.	.....
Feb. 6..	....	15	Ac.	—	Definite.	$\frac{3}{4}$	Light gray.	A few gran.	Neg.	Neg.	+ +	Bladder washed and urine collected during diuresis.
Feb. 7..	600	....	Ac.	Light.	Definite.	$\frac{1}{2}$	.....	Gran. and hyal.	Neg.	Few.	+	.....
Feb. 8..	250	....	Neut.	Moderate.	Definite.	1	.....	A few gran.	Neg.	Few.	+	.....
Feb. 9..	150	....	Ac.	Definite.	Definite.	1	.....	A few gran.	+	+	+	.....
Feb. 10..	....	8	.....	—	Definite.	....	.....	Hyal. and gran.	+	+	+	Bladder washed and urine collected during diuresis.
Feb. 12..	400	....	Ac.	Heavy.	Heavy.	1	Light green.	Hyal. and gran.	Neg.	Few.	+ +	.....
Feb. 13..	100	....	Ac.	—	Heavy.	....	.....	Few.	Neg.	Few.	Few.	.....
Feb. 14..	70	....	Ac.	Heavy.	Heavy.	2	Dark green on top.	Hyal. and gran.	—	+	+ +	.....
Feb. 15..	100	....	Ac.	Heavy.	Heavy.	$\frac{1}{5}$	.....	Few gran.	Neg.	+	+	.....
Feb. 16..	150	....	Ft. Ac.	Heavy.	Moderate.	$\frac{1}{2}$	.....	Numerous hyal. and gran.	Neg.	Very few.	Veryfew	.....
Feb. 17..	30	....	Ac.	Moderate.	Moderate.	....	.....	Few gran.	Neg.	Very few.	Few.	.....
Feb. 19..	50	....	Ac.	Moderate.	Heavy.	$\frac{1}{10}$	.....	+	Neg.	+	Neg.	.....
Feb. 20..	200	....	Alk.	Light.	Light.	$\frac{1}{10}$	White.	+	Few.	+	+	.....
Feb. 21..	37	....	Ac.	Very light.	Light.	$\frac{1}{10}$	White.	+	Neg.	+	+	.....
Feb. 22..	150	....	Ac.	Light.	Moderate.	$\frac{1}{2}$	White.	+	Neg.	+	Few.	.....
Feb. 23..	150	....	Ac.	Light.	Light.	$\frac{1}{2}$	Gray.	—	—	—	—	.....
Feb. 24..	....	22	Ac.	Faint.	Very light.	$\frac{1}{10}$	White.	+	Neg.	+	Few.	.....
Feb. 26..	260	....	Ft. Ac.	Light.	Moderate.	1	.....	Hyal. and gran.	Neg.	Very few.	Neg.	.....
Feb. 27..	135	....	Neut.	Moderate.	Moderate.	1	White.	Hyal. and gran.	Neg.	+	Few.	.....
Feb. 29..	200	....	Neut.	Light.	Light.	$\frac{1}{2}$	.....	Hyal. and gran.	Neg.	+	+	.....
Mar. 1..	100	....	Ac.	Light.	Light.	$\frac{1}{2}$	.....	Hyal. and gran.	Neg.	+	+	.....
Mar. 7..	....	45	Ac.	Light.	Moderate.	1	Light gray.	Few.	Few.	+	+	.....
Mar. 16..	....	22	Ac.	Very light.	Light.	$\frac{1}{10}$	.....	One gran.	Neg.	Few.	Few.	.....
Mar. 18..	....	12	Alk.	—	Very faint.	$\frac{1}{4}$	.....	Hyal. and gran.	Few.	+	Few.	.....
Mar. 21..	....	7	Ac.	Very faint.	—	....	.....	Few.	Few.	+ +	Few.	.....
Mar. 26..	....	9	Ac.	—	Light.	....	.....	Few.	Neg.	+	+	.....
Mar. 29..	....	10	Alk.	Very heavy.	Very heavy.	....	.....	Hyal. and gran.	Neg.	+	+	.....
Mar. 30	Operation: Ureter catheterized.											
12.30 p.m.	....	8	Ac.	Light.	Faint.	—	.....	.....	Few.	Neg.	Neg.	Urine from ureter.
1.12 p.m.	....	12	Ac.	Light.	Faint.	$\frac{1}{10}$	.....	Neg.	Few.	Neg.	Neg.	
(a).	....	60	Ac.	Light.	Faint.	1	.....	Very few gran.	Neg.	+ +	Few.	Urine from bladder.

Dog C-41.

3-5-'12. Dog, female, bull terrier, weighs 7.8 kilos (17¼ lbs.), in splendid condition.

Operation: Marble introduced into bladder.

3-16-'12. Wound healed, dog in good condition.

3-21-'12. Weighed 8.1 kilos (17¾ lbs.). Gave 500 cc. of water by stomach tube. Diuretic time 55 minutes. Animal in good condition.

3-26-'12. Gave 700 cc. of water by stomach tube and washed bladder as described. Urine collected during the 20 minutes following washing. Animal in good condition.

3-28-'12. Weighs 8.1 kilos (17¾ lbs.). Gave 500 cc. of water by stomach tube and washed bladder with negative result. Animal in good condition.

7-17-'12. Dog in good condition, weight 18 lbs. Abdominal operation. Normal saline intravenously to promote diuresis. Urine collected every ½ hr. shows albumin constantly present.

5 p. m. Death and *autopsy* at once. Right kidney is definitely hypertrophied, but surface is smooth after removal of capsule. Cortex on section is thickened. Pelvis and ureter normal. Bladder is thickened somewhat and contracted about the marble, which is frosted with deposits of gray color. There are no ulcers.

DOG C-41.

Date.	Amt. of urine in cc.		Reaction of urine.	Albumin.				Casts.	Cells.			Remarks.
1912	Cage.	Catheter.		Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.	
Mar. 5..	....	70	Ac.	Neg.	Very faint.	¼	.....	Neg.	Neg.	Neg.	Neg.	.....
Mar. 5 Operation: Marble placed in bladder.												
Mar. 9..	250	....	Ac.	Heavy.	Moderate.	2½	.....	Hyal. and gran.	Few.	Few.	Few.	.....
Mar. 16..	....	38	Ac.	—	Slight.	⅛	.....	Neg.	Neg.	Neg.	.....	.....
Mar. 18..	....	48	Alk.	Very faint.	Faint.	Tr.	.....	Few hyal.	Few.	Neg.	Neg.	.....
Mar. 19..	....	30	Ac.	Very light.	Moderate.	⅓	Dirty olive green	Few hyal.	Few.	Few.	+	.....
Mar. 21..	....	52	Ac.	Very light.	Moderate.	⅛	.....	Neg.	Neg.	Neg.	Few.	.....
Mar. 22..	530	....	Neut.	Light.	Moderate.	Neg.	.....	—	—	—	—	.....
Mar. 23..	....	15	Ac.	Light.	—	⅛	Greenish tinge.	Numerous.	+	+	+	.....
Mar. 25..	....	58	Ft. ac.	Very faint.	Moderate.	⅔	.....	+	Neg.	+	+	.....
Mar. 26..	....	40	Ac.	Light.	Moderate.	1	Light gray.	+	Neg.	+	+	.....
Mar. 26..	....	±	.....	.....	Moderate.	....	.....	.....	.....	.....	.....	Bladder washed and urine collected.
Mar. 28..	....	7	Ac.	—	Faint.	....	.....	+	Few.	Few.	+	.....
Mar. 29..	....	136	Ft. alk.	Faint.	Light.	⅛	Light gray.	Very few.	Neg.	Very few.	Few.	.....
Apr. 2..	....	13	Ac.	—	Light.	1¼	Gray.	Very few.	Neg.	Very few.	Few.	.....
Apr. 11..	....	24	Ac.	Heavy.	Moderate.	½	Dirty yellow.	Few.	Few.	+ +	Few.	.....
Apr. 15..	....	117	Alk.	Neg.	Neg.	¼	Dirty green.	Neg.	Neg.	Neg.	Neg.	.....
Apr. 20..	....	17	Ac.	—	Light.	Tr.	Light green.	Neg.	Neg.	Few.	Neg.	.....
Apr. 23..	....	95	Ac.	Neg.	Very light.	⅒	Greenish gray.	Neg.	Neg.	Neg.	Neg.	.....
Apr. 29..	....	53	Neut.	Very faint.	Light.	⅒	Light yellow.	Few.	Very few.	Neg.	Very few.	.....
May 4..	....	50	.....	.....	.....	....	.....	.....	.....	.....	.....	.....
May 4..	....	8	Ac.	—	Light.	....	.....	Neg.	Neg.	Neg.	Few.	Bladder washed and urine collected.
May 6..	....	35	Alk.	Heavy.	Heavy.	1½	Grayish green.	Neg.	Few.	+	Few.	.....
May 7..	....	65	Ac.	Light.	Moderate.	¾	White.	Neg.	Very few.	Neg.	Neg.	.....
May 7 Operation: Removal of left kidney.												
May 11..	....	55	Alk.	Moderate.	Moderate.	¼	Light gray.	Neg.	Neg.	Few.	Few.	.....
May 14..	....	93	Ac.	Light.	Light.	⅛	Gray.	Very few.	Neg.	Very few.	Few.	.....
May 16..	....	85	Alk.	Light.	Light.	⅜	Gray.	Two casts.	Neg.	Neg.	Few.	.....
May 16..	....	25	Ac.	Light.	Light.	¼	White.	+	Neg.	Neg.	+ +	Bladder washed and urine collected during diuresis.
May 18..	....	15	Ac.	Light.	Moderate.	½	Greenish tinged.	Neg.	Neg.	+	+	.....
May 24..	....	50	Ac.	Moderate.	Moderate.	⅛	Dark gray.	Neg.	Neg.	Neg.	Few.	.....
May 27..	....	29	.....	.....	.....	....	.....	.....	+ + +	.....	.....	.....
May 29..	....	30	Ac.	Heavy.	Heavy.	2	Gray.	Few hyal.	+	Neg.	Neg.	.....
July 17..												
8.15 a.m.	....	12	.....	.....	.....	2	.....	.....	Neg.	.....	.....	.....
10.45 a.m. Operation: Eck fistula produced—saline intravenously.												
11.53 a.m.	....	30	.....	.....	.....	2½	.....	.....	.....	.....	.....	.....
12.45 p.m.	....	5	.....	.....	.....	2½	.....	.....	.....	.....	.....	.....
1.45 p.m.	....	12	.....	.....	.....	2½	.....	.....	.....	.....	.....	.....
2.45 p.m.	....	20	.....	.....	.....	2½	.....	.....	.....	.....	.....	.....
3.45 p.m.	....	57	.....	.....	.....	2½	.....	.....	.....	.....	.....	.....

4-11-'12. Animal weighs 8.2 kilos (18 lbs.) and is in good condition.

4-30-'12. Weighs 8.7 kilos (19¼ lbs.), has mange.

5-4-'12. Gave 600 cc. of water by stomach tube and washed bladder as described. 8 cc. of urine collected during the following 12 minutes. Condition excellent.

5-7-'12. Operation: Removal left kidney. Weight 23 gm. Normal in gross and microscopically.

5-11-'12. Weighs 8.4 kilos (18¼ lbs.). Condition good.

5-16-'12. Weighs 8.6 kilos (18¾ lbs.). Condition excellent. Gave 700 cc. of water by stomach tube and bladder washed. 9 cc. of urine collected during the following 12 minutes.

The mucosa of fundus is normal, of base is mottled with reddish areas and indefinite nodules—a subacute cystitis.

Microscopical sections: The glomeruli, tubules and stroma are quite normal. Some of the tubules are a little dilated and contain pale, hyaline material (casts). There is no evidence of any beginning chronic nephritis. Bladder shows areas in which the epithelium is thickened. The submucosa is infiltrated with a good many mononuclear cells, some of which contain blood pigment. The blood-vessels are rather conspicuous with thickened walls. The muscle of the bladder shows definite hypertrophy.

Summary, Dog C-41.—This animal presented a very slight albuminuria before operation, but in general the observations

confirm those of the previous ones. This animal was not as sensitive to bladder irritation as many dogs, but is of interest because of the prolonged observation and a general tendency of the albuminuria to increase.

Removal of one kidney had no appreciable effect on the other organ, unless a slight amount of the albumin could be attributed to the extra work thrown upon the single organ. Autopsy showed the usual subacute cystitis, but normal ureter and pelvis with a kidney practically normal except for a uniform hypertrophy. The tubules contained a few casts, but there was no increase in connective tissue.

Dog C-54.

4-3-'12. Dog, female, mongrel, weight 7.7 kilos (17 lbs.), in good condition.

4-4-'12. Operation: Collar button sutured into bladder wall.

5.36 p. m. Catheter passed and 5 cc. of urine taken.

6.00 p. m. 2000 cc. of salt solution infused.

6.25 p. m. 3000 cc. of salt solution infused.

6.30 p. m. Urinated about 30 cc.

6.55 p. m. 3250 cc. of salt solution infused (total).

7.00 p. m. 7 cc. of urine collected and cannula taken from ureter. Kidney removed. Weighed 28 gm. Normal.

5-24-'12. Animal found dead in cage at 9.00 a. m.

12 Noon, *autopsy*. Right kidney weighed 30 gm. Normal in gross. Ureters normal. Bladder contracted, did not contain any urine. Button was firmly encapsulated in fibrous tissue on the serous surface, by the œdematous bladder wall. There was some injection of the mucosa around neck and area surrounding button. A very small calculus was found in the bladder near the button. It was about 4 mm. in length and 1 mm. in largest diameter. It was formed around a small piece of silk suture in the wall of the bladder. Chronic cystitis around area near button. Other organs normal.

DOG C-54.

Date. 1912.	Amt. of urine in cc.		Reaction of urine.	Albumin.				Casts.	Cells.			Remarks.
	Cage.	Catheter.		Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.	
Apr. 3..	..	64	Ac.	Neg.	Neg.	$\frac{3}{4}$	Brown.	Neg.	Neg.	Neg.	Neg.	Very concentrated urine.
Apr. 4..	..	28	Ac.	Neg.	Neg.	$\frac{1}{10}$	Brown.	Neg.	Neg.	Neg.	Many.	.....
Apr. 4. Operation: Button fixed in bladder wall.												
Apr. 12..	..	$4\frac{1}{2}$	Ac.	.....	.....	....	.....	Neg.	Few.	+	+	.....
Apr. 14..	..	4	Alk.	.....	.....	....	.....	Few hyal. and gran.	+	+	+	.....
Apr. 15..	..	17	Alk.	Light.	Light.	$\frac{1}{4}$	Dirty blue.	Few.	Very few.	Very few.	Few.	.....
Apr. 16..	..	3	Alk.	.....	.....	....	.....	.....	Few.	Few.	+ +	.....
Apr. 18..	65	....	Ac.	Light.	Light.	Trace.	White.	Few.	Neg.	Neg.	Few.	.....
Apr. 29..	..	2	Ac.	.....	.....	....	.....	Few.	+	+	+	.....
Apr. 30..	..	16	Ac.	Moderate.	Moderate.	$\frac{1}{10}$	Light brown	Neg.	+ +	Few.	Few.	.....
May 4..	..	4	Ac.	.....	.....	....	.....	Numerous gran.	+	Few.	Few.	.....
May 6..	..	4	Ac.	.....	.....	....	.....	Few.	+	+	Few.	.....
May 11..	..	9	Ac.	Light.	Moderate.	....	.....	Few hyal.	Neg.	Neg.	+ +	.....
May 11..	58	....	Alk.	Light.	Heavy.	$\frac{1}{2}$	White.	—	—	—	—	.....
May 16..	..	$6\frac{1}{4}$	Ac.	Light.	Light.	....	.....	.....	.....	.....	.....	.....
May 21..	..	8	Ac.	Moderate.	Light.	$1\frac{1}{2}$	White.	One hyal.	Few.	Few.	+	Bladder washed and urine collected.
May 23..	..	80	Ac.	Moderate.	Moderate.	$\frac{3}{4}$	White.	Few.	Very many.	Few.	Neg.	.....
May 23. Operation: Catheter in ureter.												
May 23..	..	7	Ac.	Moderate.	—	$1\frac{1}{2}$	White.	Few.	Very few.	Neg.	Neg.	Urine from ureter.

4-11-'12. Weighs 7.3 kilos (16 lbs.). Wound in good condition. Animal lively.

4-19-'12. Gave 500 cc. of water by stomach tube. Diuretic time 30 minutes. Weighs 7.9 kilos (17½ lbs.).

4-30-'12. Gave 500 cc. of water by stomach tube. Animal weighs 7.2 kilos (16¼ lbs.).

5-3-'12. Animal has diarrhœa and distemper.

5-11-'12. Gave 700 cc. of water by stomach tube. Animal has distemper.

5-14-'12. Gave 700 cc. of water by stomach tube and washed out bladder, but could not collect enough urine for test after washing.

5-21-'12. Gave 600 cc. of water by stomach tube, washed bladder and collected 8 cc. of urine during the 15 minutes following the washing.

5-23-'12. Operation: Catheterized left ureter about 4 cm. from pelvis of kidney.

4.50 p. m. Began infusion of salt solution into right femoral vein.

5.00 p. m. 500 cc. of salt solution infused.

5.20 p. m. 1000 cc. of salt solution infused.

5.30 p. m. Urine began to flow.

5.35 p. m. 1500 cc. of salt solution infused.

Microscopical sections: Kidney shows no abnormality of the stroma or glomeruli. Some of the tubules contain a good deal of granular coagulum, and others indefinite casts associated with a certain amount of dilatation of the lumen. Bladder shows a moderate grade of thickening of the submucosa with infiltration by mononuclear cells. The epithelial covering appears normal.

Summary, Dog C-54.—This dog differed somewhat in that the foreign body was fixed in the fundus of the bladder—a metal collar button with its broad base inside the bladder cavity, and its head in the peritoneal cavity. This operation caused a certain amount of cystitis and localized peritonitis, with a resultant albuminuria. It will be noted that the albuminuria was more pronounced following a bladder irrigation, and in general showed a tendency to increase slowly in amount. Urine obtained from the ureter at operation showed a considerable amount of albumin. Autopsy showed localized cystitis about the button and a small calculus adherent to a thread in the bladder wall. The kidneys were normal except for a few hyaline casts and slight dilatation of the tubules in places.

Dog C-59.

4-16-'12. Young female fox terrier, weight 6.8 kilos (15 lbs.), in poor condition. Unable to catheterize.

4-18-'12. Dilated vagina under ether.

4-25-'12. Dog in fair condition. Operation: Marble introduced into the bladder and a "bachelor's button" sutured into the wall of the bladder.

4-28-'12. Observed animal pass a few drops of bloody urine, and upon catheterizing the marble was dislodged from the neck of the bladder and about 20 cc. of urine drawn off.

5-13-'12. Found in cage very sick. About 25 cc. bloody fluid drawn off when catheter was introduced. Made subcutaneous injection of sterile salt solution and irrigated bladder. Died 5.00 p. m.

Autopsy, 5.10 p. m. Kidneys: Right weighs 28 gm. Left 25 gm. They are quite normal in gross. Ureters are normal. Bladder is dilated with bloody fluid, and in places the wall seems friable and partly necrotic. The mucosa is deep red mottled and greenish in places. The serous surface is injected. The urethra is practically normal. The peritoneal cavity contains 225 cc. of blood-stained fluid, and the serous surface shows beginning fibrinous inflammation. A part of this fluid certainly was derived from the urinary bladder, although no definite leak could be demonstrated at the time of autopsy.

Microscopical notes: Kidney: There is no increase in connective tissue. Glomeruli are normal. Many of the convoluted tubules contain definite casts and are dilated. One sees, too, considerable granular pink-staining material in the lumina of the convoluted tubules. The blood-vessels are widely distended. The collecting tubules and pyramids show numerous characteristic hyaline casts. The bladder shows extensive ulcers with necrosis involving the mucosa and submucosa. The submucosa is œdematous and infiltrated with great numbers of wandering cells, many of which are polymorphonuclears and show some increase in connective tissue as well. Some sections show extensive hemorrhage and œdema involving a part of the muscle coat as well.

Summary, C-59.—In this experiment a marble was placed in the bladder, and in addition a large button was fixed in the fundus of the bladder. This was associated with a high grade of albuminuria, of which a part was probably derived from the inflamed bladder mucosa. No washing of the bladder nor ureteral catheterization were accomplished, as the animal died from acute cystitis with leakage of urine into the abdomen and general peritonitis. It is of interest to note that the inflammation had not extended up the ureters in spite of obvious obstruction, and that the kidneys were free from acute inflammation. This is to be compared with the following case where an ascending infection was present. The kidneys under the microscope showed numerous hyaline casts and evidence of considerable albuminuria, but no evidence of acute or chronic nephritis. So it is very evident that much of the excreted albumin was derived from the kidney.

DOG C-59.

Date. 1912.	Amount of urine in cc.		Reaction of urine.	Albumin.				Casts.	Cells.		
	Cage.	Catheter.		Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.
Apr. 20..	....	47	Ac.	Neg.	Neg.	Trace.	Dirty gray.	Neg.	Neg.	Neg.	Neg.
Apr. 23..	....	3	Ac.	.....	.....	.....	.....	Neg.	Neg.	Neg.	Few.
Apr. 25. Operation: Foreign bodies placed in bladder wall and lumen.											
Apr. 29..	....	17	Alk.	Heavy.	Moderate.	2½	Gray.	Neg.	+ +	Few.	+
Apr. 30..	....	55	Ac.	Heavy.	Moderate.	1½	Light gray.	—	+ + +	—	—
May 7..	....	46	Alk.	Moderate.	Heavy.	1	White.	Neg.	+	+	Few.
May 11..	....	7	—	—	Moderate.	...	.....	Neg.	Neg.	+	Few.

DOG C-34

Date. 1912	Amt. of urine in cc.		Reaction of urine.	Albumin.				Casts.	Cells.			Remarks.
	Cage.	Catheter.		Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.	
Feb. 15..	....	35	Ac.	Neg.	Very faint.	½	Dirty green.	Neg.	Neg.	Neg.	Neg.	.....
Feb. 17..	....	30	Ac.	Faint.	Light.	½	Gray.	Neg.	Neg.	Neg.	+	.....
Feb. 19..	170	....	Ac.	Light.	Heavy.	¾	Gray.	Many.	Few.	+	+	Cystitis from catheter.
Feb. 20..	....	12	Ac.	—	Light.	½	.....	+	+ +	+	+	.....
Feb. 20 Operation: Marble placed in bladder.												
Feb. 22..	125	....	Ac.	Very heavy.	Heavy.	8	Drab.	.....	+ + +	.....	.....	.....
Feb. 23..	200	....	Ac.	Very heavy.	Heavy.	4	Dirty green.	.....	.....	.....	.....	.....
Feb. 24..	240	....	Alk.	—	Very heavy.	3	.....	.....	.....	.....	.....	.....
Feb. 24..	45	....	Neut.	Heavy.	Heavy.	3	.....	.....	+	+	Few.	.....
Feb. 25..	....	8	Ac.	Moderate.	Moderate.	—	.....	.....	.....	.....	.....	.....
Feb. 25..	....	55	Ft. Ac.	Moderate.	Moderate.	1½	.....	Neg.	Neg.	+ +	Neg.	.....

Dog C-34.

2-15-'12. Dog, female, mongrel, weight 5.9 kilos (13 lbs.), in good condition.

2-17-'12. 400 cc. water by stomach tube. Diuretic time 1 hour.

2-20-'12. Operation: Marble introduced into the bladder. Animal in good condition.

2-22-'12. Animal weighs 5.4 kilos (12 lbs.). Wound in good condition.

2-24-'12. Animal very sick, vomiting and diarrhœa. Wound in good condition.

2-25-'12. Animal very sick.

Operation: Made unsuccessful attempt to catheterize ureter and collect urine. About 2 cc. of blood-tinged urine was collected. Animal died 3.10 p. m.

Autopsy, 3.25. Kidneys: Pyelonephritis. Ureters: Purulent ureteritis. Bladder: Acute ulcerative cystitis. Acute local peritonitis in region of bladder and slight general peritonitis. Lungs: Œdema. Other organs normal.

Microscopical sections: Kidneys show the usual picture of suppurative pyelonephritis, with great numbers of polymorphonuclear leucocytes in large masses and columns extending throughout the cortex and medulla. In places the tubules show a good deal of injury, and again they are relatively normal. There is considerable œdema and congestion. The ureter shows a definite acute inflammation, particularly of the submucosa, and pus cells in considerable numbers are found in the lumen, in the mucosa and the œdematous submucosa. Bladder wall shows loss of substance, in places extensive hemorrhage into the submucosa associated with a great deal of œdema and numbers of wandering cells.

Summary, Dog C-34.—This dog shows a characteristic picture of acute cystitis with an ascending ureteritis, pyelitis and pyelonephritis with miliary abscesses. There was an acute localized peritonitis. It is probable that this dog was infected before operation by catheter and the foreign body intensified the inflammation, with its spread into the bladder wound and ureters. No urine was obtained from the washed bladder or ureter by catheter.

Dog C-38.

3-2-'12. Dog, male, mongrel, weight 7.7 kilos (17 lbs.), poorly nourished. Collected 8 cc. urine in beaker while animal was being anæsthetized.

Operation: Catheterized left ureter about 3 cm. from pelvis of kidney.

12.50 p. m. Started salt solution infusion, right femoral vein.

12.52 p. m. Urine started to flow.

1.04 p. m. 500 cc. salt solution infused.

1.38 p. m. 1000 cc. (total amount) salt solution injected.

Operation: Left kidney removed; it was normal. 550 cc. of urine collected from cage a few hours after operation.

3-7-'12. Animal in fair condition, weighs 7.3 kilos (16¼ lbs.). Wound broken down through skin and subcutaneous tissues.

3-21-'12. Animal weighs 7.7 kilos (17 lbs.). Wound healed. Condition fair.

3-23-'12. Operation: Catheterized right ureter about 3 cm. from pelvis of kidney.

10.55 a. m. Began infusion of salt solution into left femoral vein.

11.00 a. m. Urine started to flow.

11.05 a. m. 500 cc. of salt solution infused.

11.20 a. m. 1000 cc. of salt solution infused.

11.55 a. m. 1500 cc. of salt solution infused.

DOG C-38.

Date.	Amt. of urine in cc.		Reaction of urine.	Albumin.				Casts.	Cells.			Remarks.
1912	Cage.	Catheter.		Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.	
Mar. 2..	165	....	Ac.	Very light.	Light.	1/5	Greenish.	Hyal. and gran.	Neg.	Few.	Neg.	Spermatozoa numerous. Balanitis +.
Mar. 2..	....	8	Ac.	—	Light.	1/2	.....	Few.	Neg.	Few.	Neg.	Caught in beaker.
Mar. 2	Operation: Ureter catheterized.											
12.56 p.m.	....	3½	Neut.	.....	.....	....	.....	Neg.	+	Neg.	Few.	.....
1.02 p.m.	....	5	Neut.	Light.	Trace.	....	.....	.....	.....	.....	.....	.....
1.11 p.m.	....	10	Neut.	.....	Trace.	1/5	.....	.....	.....	.....	.....	.....
1.18 p.m.	....	10	Neut.	Light.	Trace.	—	.....	Neg.	Neg.	Neg.	Neg.	.....
1.27 p.m.	....	10	Neut.	—	Trace.	1/5	.....	.....	.....	.....	.....	.....
1.43 p.m.	....	17	Ac.	Light.	Neg.	1/5	.....	Neg.	+	+ ?	Few.	.....
5.00 p.m.	550	....	Ac.	Neg.	Very light.	Tr.	.....	Neg.	Neg.	Neg.	Neg.	Post-operative cage urine.
Mar. 5..	18	....	Alk.	Very light.	Light.	1/4	.....	+	Neg.	Neg.	Neg.	.....
Mar. 7..	140	....	Alk.	Light.	Moderate.	1/2	Pink.	Neg.	Neg.	Neg.	Neg.	.....
Mar. 8..	90	....	Ac.	Very light.	Very light.	1/2	.....	Few.	Neg.	Neg.	Neg.	.....
Mar. 9..	150	....	Ac.	Faint.	Very light.	2/3	.....	Few.	Neg.	Neg.	Neg.	Spermatozoa numerous.
Mar. 11..	60	....	Ac.	Light.	Moderate.	1	.....	.....	.....	.....	.....	.....
Mar. 23	Operation: Ureter catheterized.											
11.09 a.m.	....	4	Ac.	—	—	—	.....	.....	.....	.....	.....	.....
11.30 a.m.	....	11	Ac.	Light.	?	1/5	.....	.....	.....	.....	.....	.....
11.53 a.m.	....	11	Ac.	Light.	Light.	—	.....	.....	.....	.....	.....	.....
12.13 p.m.	....	14	Ac.	Light.	Light.	1/5	.....	A very few hyal.	+	Neg.	Neg.	.....
.....	....	50	Ac.	Heavy.	Heavy.	1½	.....	Few.	+	Neg.	Few.	Very conc. urine obtained from bladder at autopsy.

DOG S-11.

Date, 1912.	Amount of urine in cc.		Reaction of urine.	Albumin.				Casts.	Cells.		
	Cage.	Catheter.		Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.
Apr. 13..	65	....	Ac.	Very light.	Light.	1/2	Light yellow.	Few.	Neg.	Few.	Neg.
Apr. 13.	Operation: Ureter catheterized.										
12.11 p.m.	....	3	Ac.	—	Very light.	—	.....	.....	.....	.....	.....
11.35 p.m.	....	11	Ac.	—	Very light.	Trace.	White.	Neg.	Neg.	Neg.	Very few.
1.15 p.m.	....	9	Ac.	Very light.	Very light.	Trace.	White.	.....	.....	.....	.....

Animal bled to death from femoral artery. Removed bladder entire, with 50 cc. of concentrated urine.

2.00 p. m. *Autopsy.* Right kidney: Weight 40 gm. Two small infarcts were present. Otherwise the cortex was normal except for a little hypertrophy. Ureters normal. Bladder normal. Other organs normal.

Summary, Dog C-38.—This experiment and the one following serve as controls for the catheterization of the ureters. It is seen that this procedure does not call out any albuminuria. Extirpation of one kidney may cause a slight albuminuria, associated, perhaps, in part with the excess work thrown upon the other organ. Catheterization of the second ureter shows an interesting finding. The concentrated bladder urine contains much more albumin than does the urine obtained during diuresis from the ureter. The diuresis dilutes the albumin which is being excreted. It is interesting to compare this finding with those in other experiments where bladder irritation by a catheter is present and we find more albumin in the ureteral urine at this time than in that collected just previously from the bladder.

Dog S-11.

4-13-'12. Dog, male, mongrel, weight 6.4 kilos (14 lbs.), in poor condition.

Operation: Catheterized left ureter about 3 cm. from pelvis of kidney and later removed left kidney.

12.00 m. Began infusion of salt solution into right jugular vein.

12.07 p. m. Urine began to flow.

12.10 p. m. 500 cc. salt solution infused.

12.30 p. m. 1000 cc. salt solution infused.

12.50 p. m. 1400 cc. salt solution infused (total amount).

1.15 p. m. Urine collected (see table).

Operation: Left kidney removed, weight 37 gm. Normal in gross. Microscopically there is no increase in connective tissue. The glomeruli and convoluted and collecting tubules are normal.

4-18-'12. Animal weighs 6.4 kilos (14 lbs.).

4-27-'12. Animal in good condition. Wound healed excepting two or three stitch abscesses. Used for another experiment.

Dog C-50.

4-30-'12. Young dog, female, mongrel, weight 8.6 kilos (19 lbs.), in excellent condition.

5-11-'12. Weighs 8.7 kilos (19¼ lbs.). Irrigated bladder with 100 cc. of a 1 per cent silver nitrate solution in water for 10 minutes, under ether.

5-14-'12. Vagina very sensitive. Irrigated bladder with 50 cc. of a 1 per cent silver nitrate solution in water for 10 minutes, under ether. Animal not very active.

5-21-'12. Animal found very sick. Operation: Attempted to catheterize right ureter and collect urine, but animal died about 10 minutes after start.

Autopsy at once. Kidneys: The right kidney weighs 25 gm. and is normal in gross. The left kidney weighs 63 gm. and presents the characteristic picture of pyelonephritis. Its cortex is widened and streaked with opaque yellow lines containing purulent material, alternating with reddish zones of hemorrhage. The pyramids and pelvis are involved in this acute inflammation. Bladder: The mucosa is ulcerated and the bladder wall gangrenous, being of a mottled reddish green color. The serous surface of the bladder shows an acute fibrinous inflammation, but the

DOG C-50.

Date. 1912	Amount of urine in cc.		Reaction of urine.	Albumin.				Casts.	Cells.		
	Cage.	Catheter.		Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.
May 4..	....	43	Ac.	Light.	Moderate.	Trace.	White.	Neg.	+ +	+	Few.
May 10..	....	29	Ac.	Light.	Light.	Trace.	White.	Neg.	Few.	+ +	Few.
May 11..	....	72	Ac.	Very faint.	Light.	—	.....	Neg.	Neg.	+	Few.
May 11. Operation: Bladder treated with 1 per cent silver nitrate for ten minutes.											
May 14..	....	15	—	Moderate.	Light.	—	.....	.....	.....	.....	.....
May 14. Operation: Bladder treated as before.											
May 16..	....	10	Ac.	Heavy.	Moderate.	—	.....	Two casts.	+	Few.	Few.
May 16..	30	....	Ac.	Heavy.	Heavy.	2½	Drab.	—	.....	.....	.....
May 17..	675	....	Ac.	Heavy.	Heavy.	¾	Drab.	Many.	Neg.	Few.	+

DOG C-80.

Date, 1912.	Amt. of urine in cc. Catheter.	Reaction of urine.	Albumin.				Casts.	Cells.			Remarks.
			Heller's test.	Heat and acetic acid test.	Gms. per litre.	Color of Esbach ppt.		Blood.	Pus.	Epithelium.	
May 24..	50	Ac.	Light.	Moderate.	1/10	Dark gray.	Neg.	+ +	Neg.	Few.	.....
May 24. Operation: Bladder treated with 1 per cent silver nitrate solution for five minutes.											
May 29..	30	Alk.	Moderate.	Moderate.	1/5	Gray.	Neg.	+	+	Neg.	.....
May 29..	24	Ac.	Heavy.	Moderate.	1	White.	Neg.	Neg.	Neg.	Few.	Bladder washed and urine collected during diuresis.
May 30..	40	Ac.	Very light	Light.	1/10	Gray.	Few.	Few.	+	Few.	.....
a.	5	Ac.	—	Light.	—	—	Neg.	Neg.	Neg.	Neg.	Bladder washed and urine collected during diuresis.
b.	11	Ac.	Light.	—	1/3	White.	Very few.	Few.	Neg.	+	(See Notes.)

peritonitis is localized in the pelvis. The other organs are negative.

Microscopical section: Kidney shows an extreme grade of œdema, hemorrhage and infiltration of the greater part of the cortex with pus cells. Many of the tubules are destroyed. The purulent inflammation involves the tips of the pyramids and pelvis. Bladder shows extreme œdema of all its coats, with necroses involving the mucosa, submucosa and parts of the muscular coats, associated with more or less hemorrhage and great numbers of pus cells. The left ureter shows œdema of its submucous tissue with injection of the blood-vessels and numerous wandering cells, particularly polymorphonuclears.

Summary, Dog C-50.—Silver nitrate was used to produce a severe chemical cystitis, which developed into an ulcerative and gangrenous cystitis. It is curious to note that the ascending infection involved only one kidney, perhaps dependent in part on the animal's position in the cage. There is not an extreme grade of albuminuria, considering the lesions present in the bladder and one kidney.

Dog C-80.

5-24-'12. Young dog, female, collie, weighs 11.3 kilos (25 lbs.), in excellent condition.

Operation: Under ether, dilated the vagina, catheterized 50 cc. of urine and irrigated the bladder with 100 cc. of 1 per cent silver nitrate solution in water for 5 minutes. Washed bladder with 50 cc. of water immediately after.

5-29-'12. Animal weighs 11.3 kilos (25 lbs.); is not very active but in good condition otherwise. Gave 700 cc. of water by stomach tube. Diuretic time 45 minutes. Washed bladder as described, and collected urine.

5-30-'12. Gave 300 cc. of water by stomach tube and washed bladder in usual manner. 5 cc. of urine collected at end of 12 minutes after washing, and 11 cc. additional at end of 15 minutes.

6-10-'12. Animal normal and urine negative.

Summary, Dog C-80.—This experiment is of considerable interest in several respects. The chemical irritant (silver nitrate) assuredly caused a slight grade of cystitis, but this alone did not bring about a definite albuminuria during the period of observation. But when this irritated bladder mucosa was further stimulated by irrigation and catheterization, albumin appeared in the urine within a few minutes and in appreciable quantities. This albumin appeared during active diuresis and was obtained from a washed bladder. This prompt reaction can be explained only by some nervous reflex. In some instances, in normal dogs catheterized and irrigated for the first time, a similar reaction may occur, albumin appearing in a few minutes. It is possible that this reaction will be found to be constantly more marked when the bladder has been rendered hyper-irritable by chemical or other means.

It is worth noting, however, that in normal dogs catheterized for the first time an albuminuria may follow in a few hours or minutes. This reaction is not constant, and many or perhaps the majority of dogs do not give it. The albuminuria usually persists a few hours, but may last for a few days, and this may be dependent upon a slight cystitis induced by the catheterization.

SUMMARY.

The causation of a subacute cystitis by means of placing a foreign body in the lumen or wall of the urinary bladder is followed by an albuminuria of varying degree. The greater part of this albumin is derived from the renal secretion, as can be demonstrated by collecting urine from the ureter or from the washed bladder during diuresis. This renal albuminuria occurs in perfectly normal kidneys and may leave no trace of its occurrence in these normal organs, except the presence of hyaline casts and the resulting slight dilatation of the uriniferous tubules. Catheterization of the ureter without bladder irritation will cause no albuminuria. Chemical injury of the bladder mucosa may be associated with a reflex albuminuria, and in this irritated bladder some mechanical trauma (catheterization or irrigation) may be followed by a prompt and marked albuminuria. Further work is needed to determine whether this reflex albuminuria is found in human cases, but there is no reason to suppose these phenomena are limited to the urinary tract of the dog. It seems pretty clear that in these experiments on dogs we are dealing with a true nervous reflex in which stimuli applied to the bladder mucosa react with more or less promptness upon the renal epithelium and modify its secretory activity.

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NOTES ON NEW BOOKS.

A Text-Book of Practical Therapeutics. By HOBART AMORY HARE, M. D., etc. Fourteenth Edition. (*Philadelphia and New York: Lea & Febiger, 1912*)

It is a pleasure to welcome the new edition of this excellent work, one which has proved itself eminently satisfactory to a very large number of students and general practitioners. It has grown stronger and better since it appeared first twenty-two years ago, and the profession should be grateful to the author for the careful revision he has given it. It is thoroughly reliable and most useful. We congratulate Dr. Hare on its success.

Landmarks and Surface Markings of the Human Body. By L. BATHE RAWLING, M. B., B. C. (Cant.), F. R. C. S. (Eng.), etc. Illustrated. Fifth Edition. $2. (*New York: Paul B. Hoeber, 1912.*)

This small topographical anatomy is divided into five chapters covering the head and neck, the upper extremity, the thorax, the abdomen and the lower extremity. Each chapter is furnished with the plates necessary to indicate the important markings, and the text associated with the plates is so arranged by numbering each paragraph that reference between text and plate is easy. For the student whether he intends to be a surgeon or general practitioner the knowledge of such topography is all essential, and he will find this book helpful in learning his human landmarks.

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